European Journal of Neurology 2012, **19:** 360–375 doi:10.1111/j.1468-1331.2011.03501.x

EFNS GUIDELINES

EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force

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Keywords:
ALS, breaking the diagnosis, bronchial secretions, caregiver, cognitive dysfunction, drooling, Evidence-based medicine, genetic counselling, nutrition, palliative care, terminal care, ventilation

Received 16 November 2010
Accepted 12 July 2011

Background: The evidence base for the diagnosis and management of amyotrophic lateral sclerosis (ALS) is weak.

Objectives: To provide evidence-based or expert recommendations for the diagnosis and management of ALS based on a literature search and the consensus of an expert panel.

Methods: All available medical reference systems were searched, and original papers, meta-analyses, review papers, book chapters and guidelines recommendations were reviewed. The final literature search was performed in February 2011. Recommendations were reached by consensus.

Recommendations: Patients with symptoms suggestive of ALS should be assessed as soon as possible by an experienced neurologist. Early diagnosis should be pursued, and investigations, including neurophysiology, performed with a high priority. The patient should be informed of the diagnosis by a consultant with a good knowledge of the patient and the disease. Following diagnosis, the patient and relatives/carers should receive regular support from a multidisciplinary care team. Medication with riluzole should be initiated as early as possible. Control of symptoms such as sialorrhoea, thick mucus, emotional lability, cramps, spasticity and pain should be attempted. Percutaneous endoscopic gastrostomy feeding improves nutrition and quality of life, and gastrostomy tubes should be placed before respiratory insufficiency develops. Non-invasive positive-pressure ventilation also improves survival and quality of life. Maintaining the patient's ability to communicate is essential. During the entire course of the disease, every effort should be made to maintain patient autonomy. Advance directives for palliative end-of-life care should be discussed early with the patient and carers, respecting the patient's social and cultural background.

Objectives

This systematic review is an objective appraisal of the evidence regarding the diagnosis and clinical management of patients with amyotrophic lateral sclerosis (ALS). Advances in the knowledge and care of ALS warrant an updating of the 2005 EFNS guidelines [1] with the primary aim of establishing evidence-based and patient- and carer-centred guidelines for diagnosing and managing patients with ALS for clinicians, with the secondary aim of identifying areas where further research is needed.

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Background

Amyotrophic lateral sclerosis is characterized by symptoms and signs of degeneration of the upper and

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

lower motor neurons, leading to progressive weakness of the bulbar, limb, thoracic and abdominal muscles. Other brain functions, including oculomotor and sphincter function, are relatively spared, but may be involved in some patients. Cognitive dysfunction occurs in 20–50% of cases, and 5–15% develop dementia usually of frontotemporal type. Death because of respiratory failure follows on average 2–4 years after symptom onset, but 5–10% of patients may survive for a decade or more [2]. The mean age of onset is 43–52 years in familial and 58–63 years in sporadic cases of ALS [3]. The life-time risk of developing ALS is 1 in 350–500, with male sex, increasing age and hereditary disposition being the main risk factors [3–5].

Search strategy

From 2008 through February 2011, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library to date); MEDLINE-OVID (January 1966 on); MEDLINE-ProQuest; MEDLINE-EIFL; EMBASE-OVID (January 1990 on); the Science Citation Index (ISI); the National Research Register; the Oxford Centre for Evidence-based Medicine; the American Speech Language Hearing Association (ASHA); the World Federation of Neurology ALS page of reviews of published research; the Oxford Textbook of Palliative Medicine, the UK Department of Health National Research Register (www.dh.gov.uk/en/Aboutus/Researchanddevelopment/AtoZ/DH_4002357) and national neurological databases (e.g. http://www.alsa.org, http.alsod.iop.kcl.ac.uk/). There were no constraints based on language or publication status. Conflicts of interest were disclosed. Panellists were not compensated.

Method for reaching consensus

Initially, two investigators performed an independent literature search for each of 13 subjects addressed. Each pair of investigators prepared a written analysis that was communicated and discussed by email with the other members of the task force. A combined draft was then written by the chairman and circulated to the task force for further discussions. All recommendations had to be agreed to by all members of the task force unanimously.

Results

The literature concerning 13 issues in the management of ALS was evaluated by the task force. The findings were evaluated according to the recommendations of the European Federation of Neurological Societies resulting in level A, B or C recommendations [6]. Where there was lack of evidence but consensus was clear, we have stated our opinion as Good Clinical Practice Points (GCPP).

Diagnosing ALS

Diagnosing ALS is usually straightforward if the patient has progressive, generalized symptoms in the bulbar and limb regions (Table 1) [7]. Diagnosis *early* in the course of the disease when the patient has symptoms limited to one or two regions (bulbar, upper limb, trunk, lower limb) may be difficult and depends on the presence of signs in other regions and supportive findings in ancillary investigations [7–9] (class IV). The mean time from the onset of symptoms to confirmation of the diagnosis of ALS is 10–18 months [10,11] (class IV). Delays may arise if early or intermittent symptoms are unrecognized or denied by the patient, or because of inefficient referral pathways to a neurologist. There are cogent reasons for making the diagnosis as early as possible [12]. Psychologically, the absence of a definitive diagnosis, even of a disorder carrying a poor prognosis, causes distress and anxiety. Early diagnosis may obviate onerous and potentially expensive tours of the healthcare system and facilitate future planning. Early diagnosis may also provide opportunities for treatment with neuroprotective agents at a time when fewer cells are irreversibly compromised. Studies in experimental animal models and humans with *SOD1* gene mutations indicate that the loss of motor neurons is preceded by a period of cellular dysfunction [13] which may be reversible.

Our objective is to present guidelines for making the correct diagnosis as early as possible. As no single investigation is specific for ALS, and there is no

Table 1 Diagnostic criteria for ALS

The diagnosis of ALS requires the presence of: (positive criteria)
Lower motor neuron signs (including EMG features in clinically unaffected muscles)
Upper motor neuron signs
Progression of symptoms and signs
The diagnosis of ALS requires the absence of (diagnosis by exclusion):
Sensory signs
Sphincter disturbances
Visual disturbances
Autonomic features
Basal ganglion dysfunction
Alzheimer-type dementia
ALS 'mimic' syndromes (Table 3)
The diagnosis of ALS is supported by:
Fasciculations in one or more regions
Neurogenic changes in EMG results
Normal motor and sensory nerve conduction
Absence of conduction block

ALS, amyotrophic lateral sclerosis; EMG, electromyography.

Table 2 Diagnosing amyotrophic lateral sclerosis/motor neuron disease: recommended investigations

Test	Evidence class	Recommended mandatory tests	Recommended additional tests in selected cases
Clinical chemistry			
Blood			
Erythrocyte sedimentation rate	IV	x	–
C-reactive protein	IV	x	–
Haematological screen	IV	x	–
ASAT, ALAT, lactate dehydrogenase	IV	x	–
Thyroid-stimulating hormone, free T_4, free T_3 hormone assays	IV	x	–
Vitamin B_{12} and folate	IV	x	–
Serum protein electrophoresis	IV	x	–
Serum immunoelectrophoresis	IV	x	–
Creatine kinase	IV	x	–
Creatinine	IV	x	–
Electrolytes (Na^+, K^+, Cl^-, Ca^{2+}, HPO_4^{2-})	IV	x	–
Glucose	IV	x	–
Angiotensin-converting enzyme	IV	–	x
Lactate	IV	–	x
Hexoaminidase A and B assay	IV	–	x
Ganglioside GM-1 antibodies	IV	–	x
Anti-Hu, anti-MAG	IV	–	x
RA, antinuclear antibodies, anti-DNA	IV	–	x
Anti-acetylcholine receptor and anti-muscle-specific receptor tyrosine kinase antibodies	IV	–	x
Serology (*Borrelia*, virus including HIV)	IV	–	x
DNA analysis (for SOD1, SMN, SBMA, TDP43, FUS)	IV	–	x
CSF			
Cell count	IV	–	x
Cytology	IV	–	x
Total protein concentration	IV	–	x
Glucose, lactate	IV	–	x
Protein electrophoresis including IgG index	IV	–	x
Serology (*Borrelia*, virus)	IV	–	x
Ganglioside antibodies	IV	–	x
Urine			
Cadmium	IV	–	x
Lead (24-h secretion)	IV	–	x
Mercury	IV	–	x
Manganese	IV	–	x
Urine immunoelectrophoresis	IV	–	x
Neurophysiology			
Electromyography	III	x	–
Nerve conduction velocity	III	x	–
tcMEP (TMS)	IV	–	x
Radiology		–	–
Magnetic resonance imaging/computed tomography (cranial/cervical, thoracic, lumbar)	IV	x	–
Chest X-ray	IV	x	–
Mammography	IV	–	x
Biopsy			
Muscle	III	–	x
Nerve	IV	–	x
Bone marrow	IV	–	x
Lymph node	IV	–	x

sensitive and specific disease biomarker, diagnosis is based on symptoms, clinical examination findings and the results of electrodiagnostic, neuroimaging and laboratory studies (Tables 1 and 2) [14].

Great care should be taken to rule out diseases that can masquerade as ALS (Table 3) [15,16]. In specialist practice, 5–8% of apparent patients with ALS have an alternative diagnosis, which may be treatable in up to

Table 3 Diseases that can masquerade as ALS.

Anatomical abnormalities/compression syndromes
Arnold–Chiari type 1 and other hindbrain malformations
Cervical, foraman magnum or posterior fossa region tumours
Cervical disc herniation with osteochondrosis
Cervical meningeoma
Retropharyngeal tumour
Spinal epidural cyst
Spondylotic myelopathy and/or motor radiculopathy
Syringomyelia
Acquired enzyme defects
Adult GM_2 gangliosidosis (hexosaminidase A or B deficiency)
Polyglucosan body disease
Pompe's Disease (Glycogen Storage Disease type II)
Autoimmune syndromes
Monoclonal gammopathy with motor neuropathy
Multifocal motor neuropathy with/without conduction block
Dysimmune lower motor neuron syndromes (with GM_1, GD_{1b} and asialo-GM_1 antibodies)
Other dysimmune lower motor neuron syndromes, including CIDP
Multiple sclerosis
Myasthenia gravis (in particular the anti-muscle-specific receptor tyrosine kinase positive variant)
Endocrine abnormalities
Allgrove syndrome
Diabetic 'amyotrophy'
Insulinoma causing neuropathy
Hyperthyroidism with myopathy
Hypothyroidism with myopathy
Hyperparathyroidism (primary)
Hyperparathyroidism (secondary due to vitamin D deficiency)
Hypokalemia (Conn's syndrome)
Exogenous toxins
Lead (?), mercury (?), cadmium, aluminium, arsenic, thallium, manganese, organic pesticides; neurolathyrism, konzo
Infections
Acute poliomyelitis
Post-poliomyelitis progressive muscular atrophy syndrome
HIV-1 (with vacuolar myelopathy)
HTLV-1-associated myelopathy (tropical spastic paraplegia)
Neuroborreliosis
Syphilitic hypertrophic pachymeningitis
Spinal encephalitis lethargica, varicella-zoster
Trichinosis
Brucellosis, cat-scratch disease
Prion disorders
Myopathies
Cachectic myopathy
Carcinoid myopathy
Dystrophin-deficient myopathy
Inclusion body myositis
Inflammatory myopathies
Nemaline myopathy
Polymyositis
Sarcoid myositis
Neoplastic syndromes
Chronic lymphocytic leukaemia
Intramedullary glioma
Lymphoproliferative disorders with paraproteinemia and/or oligoclonal bands in the cerebrospinal fluid
Pancoast tumour syndrome
Paraneoplastic encephalomyelitis with anterior horn cell involvement
'Stiff person plus' syndromes
Physical injury
Electric shock neuronopathy
Radiation-induced radiculo-plexopathies and/myelopathy
Vascular disorders
Arterioveneous malformation
Dejerine's anterior bulbar artery syndrome
Stroke
Vasculitis
Other neurological conditions
Western Pacific atypical forms of MND/ALS (Guam, New Guinea, Kii Peninsula of Japan)
Carribean atypical forms of MND–dementia–PSP (Guadeloupe)
Madras-form of juvenile onset MND/ALS (South India)
Frontotemporal dementia with MND/ALS (including Pick's disease with amyotrophy)
Multiple system atrophy
Olivo-ponto cerebellar atrophy syndromes
Primary lateral sclerosis (some subtypes not related to ALS)
Progressive encephalomyelitis with rigidity
PSP
Hereditary spastic paraplegia (many variants, some subtypes with distal amyotrophy)
Progressive spinal muscular atrophy (some subtypes not related to ALS)
Spinobulbar muscular atrophy with/without dynactin or androgen receptormutation
Spinal muscular atrophy I–IV
Brown–Vialetto–van Laere syndrome (early-onset bulbar and spinal ALS with sensorineural deafness)
Fazio–Londe syndrome (infantile progressive bulbar palsy)
Harper–Young syndrome (laryngeal and distal spinal muscular atrophy)
Monomelic sporadic spinal muscular atrophy (benign focal amyotrophy, including Hirayama syndrome)
Polyneuropathies with dominating motor symptoms (like hereditary motor and sensory neuropathy type 2, hereditary motor neuropathy type 5)
Familial amyloid polyneuropathy
Benign fasciculations
Myokymia

ALS, amyotrophic lateral sclerosis; MND, motor neuron disease; PSP, Progressive supranuclear palsy.

50% of the cases [16–19] (class IV). An evolution of atypical symptoms and a lack of progression of typical symptoms are the most important 'red flags' suggesting an alternative diagnosis [16]. The diagnosis should be regularly reviewed [18,19]. The revised El Escorial criteria [20, summarized in Table 4] are excessively restrictive and are not designed for use in routine clinical practice [21]. The new Awaji electrodiagnostic algorithm [22] added to the El Escorial criteria improves diagnostic sensitivity with no loss in specificity [23] and improves early diagnosis as shown in several class IV studies [24–27]. The clinician must decide, on the balance of probability, whether or not the patient has ALS, even in the absence of unequivocal

Table 4 The Revised El Escorial research diagnostic criteria for ALS with the Awaji electrodiagnostic algorithm included – a summary (Modified from [20] and [22])

Clinically definite ALS
UMN and LMN clinical signs or electrophysiological evidence in three regions
Clinically definite ALS – laboratory supported
UMN and/or LMN clinical signs in one region *and* the patient is a carrier of a pathogenic SOD1-gene mutation
Clinically probable ALS
UMN and LMN clinical or electrophysiological evidence by LMN and UMN signs in two regions with some UMN signs rostral to the LMN signs
Clinically possible ALS
UMN and LMN clinical or electrophysiological signs in one region only, or
UMN signs in at least two regions, or
UMN and LMN signs in two regions with no UMN signs rostral to LMN signs. Neuroimaging and laboratory studies (Table 2) have excluded other diagnoses.

ALS, amyotrophic lateral sclerosis; EMG, electromyography; LMN, lower motor neuron; UMN, upper motor neuron.

upper and lower motor neuron signs [28]. Experience suggests that pursuing an early diagnosis of ALS outweighs the potential increase in risk of misdiagnosis (GCPP).

Recommendations

1. The diagnosis should be pursued as early as possible. Patients in whom ALS is suspected should be referred with high priority to an experienced neurologist (GCPP).

2. All suspected new cases should undergo prompt detailed clinical and paraclinical examinations (see Tables 1 and 2) (GCPP).

3. In some cases, additional investigations may be needed (see Table 2).

4. Repetition of the investigations may be required if initial tests are equivocal (GCPP).

5. Review of the diagnosis is advisable if there is no evidence of typical progression or the patient develops atypical features (see Table 1) (GCPP).

Breaking the news: communicating the diagnosis

Imparting a diagnosis of ALS requires skill. If not performed appropriately, the effect can be devastating, leaving the patient with a sense of abandonment and destroying the patient–physician relationship [29] (class III). More than half of surveyed patients and caregivers state that they are dissatisfied by the manner in which the diagnosis has been communicated [29,30] (class IV). Studies of other fatal illnesses [31] demonstrate advantages in using specific techniques such as those outlined in Table 5 [32]. Patients/caregivers are more satisfied if

Table 5 How should a physician tell patients that they have ALS?

Task	Recommendations
Location	Quiet, comfortable and private
Structure	In person, face-to-face
	Convenient time (at least 45–60 min)
	Enough time to ensure there is no rushing or interruptions
	Make eye contact and sit close to the patient
Participants	Know the patient *before* the meeting, including the family, emotional and social situation, case history, and all relevant test results. Have all the facts at hand.
	Have the patient's support network present (relatives), it is often an advantage that the patients network 'outnumber' the hospital staff present at the meeting. Have a clinical nurse specialist or social counsellor available.
What is said	Find out what the patient already knows about the condition
	Ascertain how much the patient wants to know about ALS and tailor your information accordingly
	Give a warning comment that bad news is coming.
	The whole truth may need to come by instalments
	Use the correct ALS-term, not 'wear and tear of the motor nerves'
	Explain the anatomy of the disease (make a simple drawing)
	If the patient indicates that they want to know the course of the disease, be honest about the likely progression and prognosis, but give a broad time frame and recognise the limitations of any predictions
	Say that there is currently no cure and symptoms tend to steadily worsen
	Mention that prognosis is highly variable and that some patients survive for 5, 10 or more years
	Acknowledge and explore the patient's reaction and allow for emotional expression
	Summarise the discussion verbally, in writing, and/or on an audiotape
	Allow time for questions
Reassurance	Acknowledge that this is devastating news, but discuss reasons for hope such as research, drug trials and the variability of the disease
	Explain that the complications of ALS are treatable
	Reassure that every attempt will be made to maintain the patient's function and that the patient's treatment decisions will be respected
	Reassure that the patient will continue to be cared for and will not be abandoned
	Inform about patient support groups (offer contact details and leaflets)
	Inform about neuroprotective treatment (i.e. riluzole) and ongoing research
	Discuss opportunities to participate in research treatment protocols (if available)
	Acknowledge a willingness to get a second opinion if the patient wishes
How it is said	Emotional manner: warmth, caring, empathy, respect
	Be honest and sympathetic, but not sentimental
	Give news at the person's pace; allow the patient to dictate what he or she is told

Table 5 (*Continued*)

Task	Recommendations
Language	Simple and careful word choice, yet direct; no euphemisms or medical jargon

Modified from [1].

effective communication strategies are used, and more time is spent discussing the diagnosis [30,33] (class IV). Callous delivery of the diagnosis may affect the families'/carers' psychological adjustment to bereavement later [34] (class IV).

Recommendations

1. The diagnosis should be communicated by a consultant with a good knowledge of the patient (GCPP).
2. The physician should start the consultation by asking what the patient already knows or suspects (GCPP).
3. The diagnosis should be given in person, ensuring enough time for discussion (suggest at least 45–60 min). Provide printed materials about the disease, about support and advocacy organizations and informative websites. A copy letter summarising the discussion can be helpful for patients and carers (GCPP).
4. Assure patients that they will not be 'abandoned' by healthcare services and will be supported by a professional ALS care team (where available), with regular follow-up visits to a neurologist. Make arrangements for a first follow-up visit, ideally within 2–4 weeks (GCPP).
5. Avoid the following: withholding the diagnosis, providing insufficient information, imposing unwanted information, delivering information callously, taking away or not providing hope (GCPP).

Multidisciplinary care

Specialist multidisciplinary clinics (tertiary centres) can provide optimized diagnostic and management services for patients with ALS [28,32,35,36]. Comparisons between clinic-based cohorts and population-based cohorts of patients have confirmed a referral bias: patients attending multidisciplinary clinics tend to be younger and to have had symptoms for longer than those who do not [35–39] (Class II). An independent survival benefit has been identified in two studies (Class II) [36,38], more relevant in bulbar patients, whilst another study has shown no effect [39]. Patients attending multidisciplinary clinics have fewer hospital admissions and shorter inpatient stays than those who attend general clinics [36] (Class II). The increased use of riluzole and non-invasive ventilation, attention to nutrition and earlier referral to palliative care services are likely to contribute to the increased survival of those attending multidisciplinary clinics [36,38,40,41]. Tertiary centres can also increase quality of life of patients with ALS (class III), perhaps related to a greater provision of appropriate aids and appliances [40,42,43].

Recommendations

1. Multidisciplinary care should be available for people affected by ALS. Attendance at multidisciplinary clinics may extend survival, decrease medical complications (level B) and improve quality of life (level C).
2. The following specialists should be part of or readily available to the multidisciplinary clinic team: neurologist, respiratory physician, gastroenterologist, rehabilitation medicine physician, social counsellor, occupational therapist, speech therapist, respiratory therapist, specialized nurse, physical therapist, dietitian, psychologist, dentist and palliative care physician (GCPP).
3. Patients should generally be reviewed every 2–3 months, although they may require more frequent review in the months following diagnosis or in the later stages of disease, and less frequent review if their disease is progressing slowly. The patient support team should maintain regular contact with the patient and relatives between visits (GCPP).
4. Ideally, the patient should be followed by the same neurologist liaising closely with the patient's primary care physician (family general practitioner) (GCPP).
5. Effective channels of communication and co-ordination are essential between the hospital-based multidisciplinary clinic team, the primary healthcare sector, the palliative care team and community services (GCPP).

ALS caregivers and burden of care

ALS causes progressive loss of independence and an increased need for help with activities of everyday life. Carers progressively increase the time they devote to caring [44]. The caregivers' burden relates to personal and social restrictions and to psychological and emotional problems (Class IV) [45,46]. Caregivers frequently search for information about ALS, and many actively participate in interactions between the patient and physician, from the time of diagnosis through to decision-making regarding advance directives and end-of-life care. Certain ALS symptoms cause particular strain in carers. If the patient loses effective communication, carers can become intellectually and emotionally isolated. The use of augmentative alternative communication devices can help to restore communication. Several studies have shown that the provision of mechanical ventilation for patients causes

particular strain on caregivers, reducing their quality of life and raising their responsibilities related to managing the ventilator and providing for the increasing caring costs (Class IV) [47–49]. Sexuality may be a problematic issue for many ALS patient–caregiver couples. Reported problems include decreased libido, passivity of the partner and the carer's own passivity. The most frequent reasons cited were the physical weakness and the body image changes because of ALS (Class IV) [50].

Half of patients with ALS in a cohort from the UK and Germany died at home [51]. The anticipation of patients' imminent deaths may increase caregiver distress and anxiety. However, Neudert *et al.* report that most patients with ALS die peacefully and no patient 'chokes to death' if good palliative care measures are in place (Class IV) [51].

Some caregivers go through a grieving process starting from the time that diagnosis is given [52,53]. Anticipation of future loss is as important as the loss itself in leading to psychological difficulties. Caregivers risk feelings of burn out, repercussions from forced changes in living arrangements and financial hardships [53,54].

Recommendations

1. Caregivers should be acknowledged in their double role in the disease process: they are the most important resource for the patient, yet they are affected themselves, and their own needs as carers need to be addressed (GCPP).
2. Ideally, caregivers should be involved from the time of diagnosis, whilst preserving patients' autonomy (GCPP).
3. Carers' own health needs should be considered. Physical, psychological and spiritual support should be provided when needed (GCPP).
4. Maintaining communication between patients and caregivers is important (GCPP).
5. The likelihood of a peaceful death process should be communicated to patients and their caregivers/relatives (GCPP).
6. Bereavement counselling and support should be offered to all caregivers (GCPP).

Neuroprotective treatment/disease-modifying treatment

To date, riluzole is the only drug that has been shown to slow the course of ALS in four Class I studies [55–58]; a Cochrane review has also been published [59]. Oral administration of 100 mg riluzole daily improved the 1-year survival by 15% and prolonged survival by ≈3 months after 18 months' treatment. There was a clear dose effect. Eleven people needed to be treated with riluzole to delay one death for 12 months. These studies did not include patients with early disease. Later, retrospective Phase IV studies from five clinical databases indicate that the overall gain in survival (i.e. over the whole extent of the disease course) may extend from 6 (Class III) [60], 10 (Class IV) [61], 12 (Class IV) [62], 14 (Class IV) [63] or 21 (Class IV) [64] months, although these estimates are almost certainly subject to statistical biases. The drug is safe, with few serious side effects. Fatigue was a side effect in 26% of patients taking riluzole compared with 13% receiving placebo (number needed to harm = 8) [55]. Although patients with progressive muscular atrophy or primary lateral sclerosis were not included in the riluzole trials, pathological and genetic studies show that some patients with progressive muscular atrophy and primary lateral sclerosis fall within the ALS syndrome, so may benefit from the drug [16,65] (Class IV). Riluzole may have little effect in late-stage ALS, and it is not clear whether and when treatment should be terminated. A large number of other drugs have been tested in ALS, unfortunately with negative results (Table 6).

Recommendations

1. Patients with ALS should be offered treatment with riluzole 50 mg twice daily (level A).
2. Treatment should be initiated as early as possible after diagnosis (GCPP). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (GCPP).
3. Patients with progressive muscular atrophy, primary lateral sclerosis or hereditary spastic paraplegia should as a rule not be treated with riluzole (GCPP).
4. Irrespective of familial disposition, all patients with a symptomatic progressive MND and carrying a *SOD1* gene mutation should be offered treatment with riluzole (GCPP).
5. Currently, there is insufficient evidence to recommend treatment with vitamins, testosterone, antioxidants such as co-enzyme Q-10 and gingko biloba, intravenous immunoglobulin therapy, cyclosporin, interferons, Copaxone, KDI tripeptide, neurotrophic factors (including BDNF, IGF-1 and mecasermin rinfabate), ceftriaxone, creatine, gabapentin, minocycline, stem cells or lithium (GCPP).

Symptomatic treatment

Symptomatic treatment aims to improve the quality of life of patients and caregivers. Symptoms should be treated as they become prominent and incapacitating.

Sialorrhoea

Sialorrhoea (drooling or excessive salivation) is common and may be socially disabling. Amitriptyline is

Table 6 Summary of the most important controlled therapeutic studies in amyotrophic lateral sclerosis

Completed trials
N-Acetylcysteine*
Brain-derived neurotrophic factor*
Branched-chain amino acids*
Buspirone*
Celecoxib*
Ciclosporin*
Ciliary neurotrophic factor*
Co-enzyme Q10*
Copaxone*
Creatine*
Dextromethorphan*
Gabapentin*
Glial-derived neurotrophic factor*
IGF-1*
Indinavir*
Interferon-beta-1a*
Lamotrigine*
Lithium*
Lymphoid irradiation*
Memantine*
Minocyclin*
Nimodipine*
ONO-2506*
Oxandrolone*
Pentoxifylline*
Riluzole
Selegiline*
Talampanel*
TCH346*
Thalidomide*
Topiramate*
Valproic acid*
Verapamil*
Vitamin E*
Xaliproden*
Ongoing Phase II/III trials (2009–2011)
Arimoclomol
Ceftriaxone
Cistanche total glycosides
Combination therapy (celecoxib, creatine, minocycline)
Edaravone
Granulocyte colony-stimulating factor
Growth hormone
R(+) pramipexole (KNS-760704)
Mecobalamin
Olanzapine
Olesoxime
Pioglitazone
Pyrimethamine
SB-509
SOD1 DNA antisense oligonucleotides
Tauroursodeoxycholic acid
Phase III trials being planned or considered
AEOL 10150
Celastrol
IGF-1 – viral delivery
NAALADase inhibitors
Nimesulide
Ritonavir and hydroxyurea
Sodium phenylbutyrate
Scriptaid
Intracerebroventricular delivery of VEGF

IGF-1, Insulin-like growth factor.
*No therapeutic benefit was observed.

often used, but there are no formal studies proving its efficacy [66]. Oral doses of 10 mg three times a day are often sufficient. Atropine drops, 0.5% or 1%, administered three or four times a day sublingually have the advantage of a short duration of action – valuable in patients who suffer from sialorrhoea alternating with an uncomfortably dry mouth. Glycopyrrolate (in nebulized or i.v. form) has been shown to be effective in patients with Parkinson's disease [67] (Class I), but there are no studies in ALS. Transdermal hyoscine (scopolamine), 1.5 mg every third day, reduces salivary flow (Class IV) [68,69]. Care is needed in elderly patients, because of the frequent side effects of confusion or loss of bladder control. Studies with botulinum toxin (type A) (Class IV) [70–72] and a single randomized trial with botulinum toxin type B (Class I) [73] injected into the salivary glands reduced saliva in patients with refractory sialorrhoea. The injections were well tolerated. Caution is needed in patients with significant bulbar palsy as increased dysphagia may occur, with serious consequences [74]. Another option is external irradiation of the salivary glands, with four studies showing satisfactory results (Class IV) [75–78]. Surgical interventions may lead to problematic effects such as increased secretion of thick mucus [79].

Recommendations

Treat sialorrhoea in ALS with amitriptyline, oral or transdermal hyoscine, or sublingual atropine drops (GCPP).

1. In patients with refractory sialorrhoea, botulinum toxin injections into the parotid and/or submandibular gland are effective and generally well tolerated (level B for botulinum toxin type B, level C for type A toxin).

2. Irradiation of the salivary glands may be tried when pharmacological treatment fails (GCPP).

3. Surgical interventions are not recommended (GCPP).

Bronchial secretions

Patients with bulbar or respiratory insufficiency commonly report difficulties in effectively clearing tenacious sputum, and mucus accumulation is a negative prognostic factor in patients with ALS treated with non-invasive ventilation [80]. The mucosa of the nasal cavity, larynx, trachea, bronchial airways and lungs

contribute a constant flow of serous and mucoid fluids. Medication with mucolytics like guaifenesin or *N*-acetylcysteine, a beta-receptor antagonist (such as metoprolol or propranolol) [81] (Class IV), and/or an anticholinergic bronchodilator like ipratropium and/or theophylline, or even furosemide, may be of value, but no controlled studies in ALS exist. Mechanical cough-assisting devices (insufflator–exsufflator) via a face mask have been effective in patients with ALS in uncontrolled trials [82,83] (Class IV).

Recommendations

1. A mucolytic including *N*-acetylcysteine, 200–400 mg three times daily, may be beneficial (GCPP).
2. Beta-receptor antagonists and a nebulizer with saline and/or an anticholinergic bronchodilator and/or a mucolytic and/or furosemide may be used in combination. Mucolytics should only be used if sufficient cough flow is present (GCPP).
3. The patient and carer should be taught the technique of assisting expiratory movements using a manual-assisted cough (can also be performed by a physical therapist) (GCPP).
4. The use of a mechanical insufflator–exsufflator may be helpful, particularly in the setting of an acute respiratory infection (GCPP).
5. A portable home suction device and a room humidifier may be of use (GCPP).

Pseudobulbar emotional lability

Emotional lability occurs in at least 50% of patients with ALS irrespective of the presence or absence of bulbar motor signs [84]. Emotional lability does not correlate with cognitive impairment [85]. Prominent pseudobulbar features such as pathological weeping, laughing or yawning can be socially disabling and affect patients'quality of life. The most commonly used agents are tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), which were effective in small placebo-controlled studies or case series [86,87] (Class IV). Two randomized controlled trials of a fixed dose combination of dextrometorphan and quinidine have shown efficacy in improving emotional lability and quality of life [88,89] (Class I). This medication has been approved by the US FDA.

Recommendations

1. Inform the patient and relatives that emotional lability is not a sign of an additional mood disorder but is because of the effects of ALS on the brain (GCPP).
2. Troublesome emotional lability should be treated (GCPP). Antidepressants such as amitriptyline (in particular in patients with drooling), fluvoxamine and citalopram are usually sufficient (level C).
3. A combination of dextrometorphan and quinidine has been shown to be effective (level A).

Cramps

Cramps may be a troublesome symptom, particularly at night. A single randomized controlled trial with tetrahydrocannnabinol failed to show efficacy in patients with ALS with moderate to severe cramps [90] (Class I). Levetiracetam was beneficial in an open-label small pilot study [91] (Class IV). Quinine sulphate has been banned by the FDA because of safety concerns [92]. However, a recent Cochrane Review in non-ALS cramps found quinine sulphate to be effective with no difference serious adverse events between the placebo and active drug [93]. Treatments such as massage, physical exercise, hydrotherapy in heated pools, carbamazepine, diazepam, phenytoin and verapamil have been tried, but there are no controlled studies in ALS.

Recommendations

1. Levetiracetam may be tried. If unsuccessful or side effects, quinine sulphate (200 mg twice daily) may be of benefit (GCPP).
2. Physiotherapy, physical exercise and/or hydrotherapy may be helpful (GCPP).

Spasticity

Physical therapy is the mainstay of treatment of spasticity in ALS and has been found effective (Class III) [94]. Other interventions such as hydrotherapy, heat, cold, ultrasound, electrical stimulation, chemodenervation and in rare cases surgery have been used, although no controlled studies in ALS exist. In patients with ALS, intractable spasticity, and associated pain, intrathecal baclofen was more effective than oral medication and greatly improved patients' quality of life (Class IV) [95,96]. Although not formally tested in ALS, in clinical practice, gabapentin (900–2400 mg daily), tizanidine (6–24 mg daily), memantine (10–60 mg daily), dantrolene (25–100 mg daily), tetrazepam (100–200 mg daily) and diazepam (10–30 mg daily) have been used. Botulinum toxin A has successfully been used to treat trismus and stridor in single cases [97].

Recommendations

1. Regular physical therapy can help relieve significant spasticity (GCPP).
2. Antispastic drugs such as baclofen and tizanidine may be tried (GCPP).
3. If spasticity is severe despite oral medications, intrathecal baclofen may be helpful (GCPP).
4. Hydrotherapy with exercises in warm pools (32–34°C) and cryotherapy may be considered (GCPP).

Depression and anxiety

Depression and anxiety occur frequently in patients with ALS and their caregivers [98]. Anxiety is particularly prevalent during the diagnostic and terminal phases [99]. No formal studies with antidepressants have been conducted in patients with ALS, but empirically tricyclic antidepressants (e.g. amitriptyline) and SSRIs such as escitalopram may be effective. Mirtazapine may be better tolerated in the later stages than SSRIs or amitriptyline. The choice may be guided by additional symptoms (e.g. sialorrhoea, insomnia, apathy, appetite loss), which are differently affected by the various antidepressants. There are no systematic studies on anxiolytics in ALS. Some antidepressants, such as escitalopram, exert anxiolytic effects, but additional oral diazepam or sublingual lorazepam, may be necessary.

Recommendations

1. Treat depression in ALS with an appropriate antidepressant, for example amitriptyline, an SSRI, or mirtazapine. SSRI may be preferably in elderly or cognitively impaired patients (GCPP).
2. Treat anxiety with bupropion or benzodiazepines such as diazepam tablets or suppositories, Temesta tablets 0.5 mg two or three times daily, or sublingual lorazepam (GCPP).

Insomnia and fatigue

Insomnia is common in the final months of life in patients with ALS [100]. There are likely to be several causes, including depression, cramps, pain and respiratory distress, which if identified should be treated. For insomnia in ALS, amitriptyline and zolpidem are the most commonly used medications [66]. Fatigue is a frequent and potentially debilitating symptom. It may be of central and/or peripheral origin [100]. One open-label study and one small Class I study with modafinil revealed a significant reduction of fatigue with a number-needed-to-treat of 1.6 [101,102]. However, the long-term effects in ALS have not yet been studied.

Recommendations

1. Treat insomnia with amitriptyline, mirtazapine or appropriate hypnotics (e.g. zolpidem) (GCPP).
2. For debilitating fatigue, modafinil may be considered (level A).

Venous thrombosis

Patients with ALS have an increased risk of deep venous thrombosis (DVT), with an annual incidence rate of at least 2.7% [103,104]. The increased risk correlates with greater immobility and impaired respiratory function, but is independent of the patient's age. There are no studies regarding the management of DVT in patients with ALS.

Recommendations

1. DVT should be treated with anticoagulants (GCPP).
2. The optimum management of risk factors for venous thrombosis should be pursued. Physiotherapy, limb elevation and compression stockings are recommended (GCPP).
3. There is currently insufficient evidence to recommend prophylactic medical treatment with anticoagulants.

Unproven therapies

Patients with ALS frequently use complementary and alternative medicines (CAM) suchs as vitamins, herbal supplements, homoeopathy and acupuncture [105]. Series of Class IV trials have tested interferon-alfa [106], human recombinant SOD1 [107], ciliary neurotrophic factor [108], brain-derived neurotrophic factor [109] and similar drugs, all without evidence of clinical benefit. Insulin-like growth factor-1 has been injected intrathecally safely, with a modest clinical effect reported [110] (Class IV). In randomized, controlled and open studies, liquorpheresis (filtration of cerebrospinal fluid) has been performed in 11 patients with ALS, without clinical effect [111,112] (Class IV). A Phase 1 safety study of hyperbaric oxygen therapy reported some efficacy on fatigue in four of five patients with ALS [113], whilst a phase II study was reported as negative [114] (Class IV). Repetitive transcranial magnetic stimulation of the motor cortex had a beneficial effect in a pilot trial (Class IV) [115] but did not delay functional deterioration in a double-blind placebo-controlled study in 20 patients [116] (Class III).

Stem cell therapy is still in experimental development in ALS. The intravenous, intrathecal or intraparenchymal administration of haematopoietic stem cells derived from peripheral blood or bone marrow has been tested in small series of patients [117–122] (Class IV). Even if these procedures are safe in the short term, the studies to date have not yielded sufficiently robust data to allow translation to clinical practice [123]. Clinical efficacy is unproven, and long-term safety still needs to be demonstrated.

A number of patients with ALS have, in a non-scientific setting, received intracerebral transplantation of olfactory ensheathing cells [124,125], resulting in serious side effects in some [126] (Class IV).

Recommendations

1. Before cellular therapies become a reality, a more thorough preclinical evaluation and elucidation of several open questions is mandatory (GCPP).

2. No well-designed clinical trials testing cellular therapies have as yet been completed demonstrating safety and clinical efficacy supported by pathological evidence in a sufficient number of patients.
3. Patients with ALS should be carefully informed about existing reliable data related to cell therapies. All current treatments with cell transplantation are purely experimental, and there is no proven effect on disease outcome. If they decide to undergo transplantation, thorough examination before and after the stem cell treatment should be performed and documented to improve the knowledge of benefits and/or side effects (GCPP).
4. Accurate and unbiased information related to cell therapies and other unproven/alternative therapies needs to be delivered to the patient community (GCPP).
5. All procedures involving the injection and transplantation of stem cells to a patient with ALS should be considered experimental and should be approved by a medical research ethical review board and performed in full accordance with the Declaration of Helsinki (WMA, 1964) (GCPP).

Genetic testing and counselling

In different populations, the frequency of familial ALS is between 5 and 23% of all ALS cases [2,3,127]. Since 1993, mutations in ten genes – *SOD1*, *VAPB*, *SETX*, *ALSIN, ANG*, *FUS, TARDBP, ATXN2, OPTN* and *VCP* – have been associated with ALS (http://alsod.iop.kcl.ac.uk/als/). Mutations in the latter nine genes appear to be rare, it is unclear whether all reported mutations are pathogenic, and analysis of these genes is at present usually only performed in research settings. A few patients (often diagnosed as sporadic ALS) with mutations in other genes have also been reported, but causation remains to be proved. Since 1993, 164 mutations have been reported in the *SOD1* gene (http://alsod.iop.kcl.ac.uk/als/). The most frequent mutation is the D90A, which in many European countries is inherited as a recessive trait with a characteristic slowly progressing phenotype, although pedigrees with dominantly (heterozygous) inherited D90A-*SOD1* and an aggressive phenotype have also been reported [65,128]. Around 12–23% of patients diagnosed with familial ALS carry a *SOD1* mutation [127]. *SOD1, FUS* and *TARDBP* mutations have been described in a small proportion of apparently sporadic patients with ALS, suggesting that some mutations have reduced disease penetrance [http://alsod.iop.kcl.ac.uk/als/, 65,127–130]. A DNA *SOD1* diagnostic test speeds up the diagnostic process and can be of help in diagnosing patients with atypical features [65,127,130], as well as providing some prognostic information [http://alsod.iop.kcl.ac.uk/als/, 127] (Class IV). There is no specific therapy for patients with *SOD1* gene mutations, but three clinical trials targeting *SOD1* specifically are currently underway. Presymptomatic (predictive) genetic testing is possible but is a sensitive issue with emotional, ethical and legal implications that must be addressed before analysis should take place [131]. Special consideration should be taken before presymptomatic testing is performed in familial ALS families where the mutation is associated with reduced disease penetrance or variable prognosis (Class IV) [65,127,130].

Recommendations
1. In all patients with suspected ALS, progressive muscular atrophy, primary lateral sclerosis or frontotemporal dementia, a detailed medical history of the patient, siblings, parents and grandparents and their siblings should be obtained to potentially disclose a familial disease with reduced disease penetrance (GCPP).
2. Clinical DNA analysis for gene mutations should only be performed in cases with a known family history of ALS, and in sporadic ALS cases with the characteristic phenotype of the recessive D90A mutation (GCPP).
3. Clinical DNA analysis for gene mutations should *not* be performed in cases with sporadic ALS with a typical classical ALS phenotype (GCPP).
4. In familial or sporadic cases where the diagnosis is uncertain, SMN, androgen receptor or *TARDBP, FUS, ANG* or *SOD1* DNA analysis may accelerate the diagnostic process (GCPP).
5. Before blood is drawn for DNA analysis, the patient should receive genetic counselling. Give the patient time for consideration. DNA analysis should be performed only with the patient's informed consent (GCPP).
6. Presymptomatic genetic testing should only be performed in first-degree adult blood relatives of patients with a known gene mutation. Testing should only be performed on a strictly voluntary basis as outlined (Table 7) and should follow accepted ethical principles (GCPP).
7. Results of DNA analysis performed on patients and their relatives as part of a research project should not be used in clinical practice or disclosed to unaffected relatives. The research results should be kept in a separate file and not in the patient's standard medical chart (GCPP).

Respiratory management in patients with ALS

Respiratory complications are the main cause of death in ALS (Fig. 1), primarily as a consequence of diaphragmatic weakness combined with aspiration and infection [132]. Erect forced vital capacity and vital

Table 7 Guidelines for presymptomatic genetic testing amyotrophic lateral sclerosis

1. The test subject should belong to a family with a known *SOD1, FUS* or *TARDBP* gene mutation
2. The test subject should be a first-degree relative of an affected blood relative, or a second-degree relative of an affected case if the first-degree relative is deceased
3. The test subject should be 18 years or older
4. The test subject should be mentally and physically healthy
5. The test subject should not be under emotional stress (e.g. recently married or divorced, has become unemployed, pregnant, etc.)
6. The test subject should participate as a volunteer without influence from a third party
7. The test subject should receive a minimum of two genetic counselling sessions before the blood is drawn
8. The test subject can request more than two genetic counselling sessions
9. Genetic counselling should be given by professionals with a specific knowledge about amyotrophic lateral sclerosis and genetics
10. After the blood sample has been drawn, the mutation analysis should be performed as quickly as possible to minimise the emotional discomfort of the procedure
11. The test subject should be informed of the test result at a personal meeting with a genetic counsellor. The test result should never be given by letter or electronic communication
12. It is advisable that the test subject be accompanied by a close friend at the genetic counselling sessions and when the test result is announced
13. The test subject can at any time demand that the blood sample and test records be destroyed
14. The test subject can at any time and without explanation withdraw from the test procedure and choose not to be informed of the test result
15. Professional and community resources should be available to deal with the impact of the test result on the test subject and relatives
16. The test result is private and should be kept in a separate file in the medical chart
17. The test result is private, and no third party can request taking part in the result (unless regulated otherwise by national legislation)

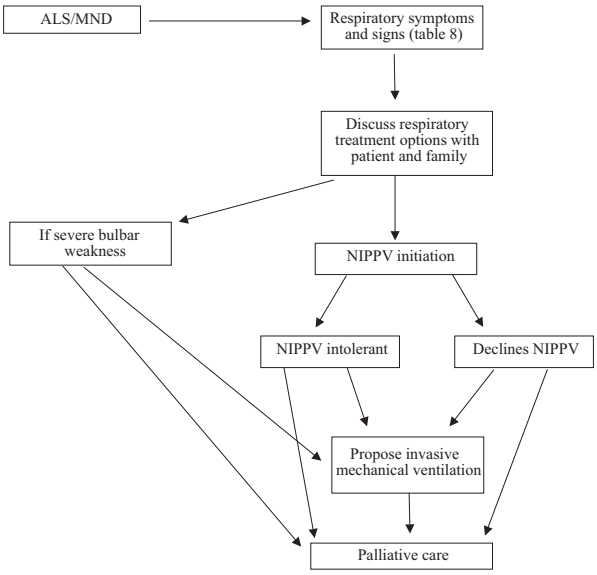

Figure 1 Flowchart for the management of respiratory dysfunction in amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). NIPPV, non-invasive positive pressure.

capacity are the most widely used tests to evaluate respiratory function and should be performed regularly, along with an assessment of symptoms suggestive of respiratory insufficiency (Table 8). Sniff nasal pressure (SNP) may be more accurate in patients with weak lips, but neither forced vital capacity nor SNP is a sensitive predictor of respiratory insufficiency in patients with severe bulbar involvement [133]. Percutaneous nocturnal oximetry is an easy tool to screen patients with and can be useful to determine the need for non-invasive positive-pressure ventilation (NIPPV) [134]. Phrenic nerve responses may predict hypoventilation in ALS [135]. Blood gas abnormalities are generally a late finding. Cough effectiveness can be assessed by measuring peak cough flow [136].

Table 8 Symptoms and signs of respiratory insufficiency in amyotrophic lateral sclerosis

Symptoms	Signs
Dyspnoea on minor exertion or talking	Tachypnoea
Orthopnoea	Use of auxilliary respiratory muscles
Frequent nocturnal awakenings	Paradoxical movement of the abdomen
Excessive daytime sleepiness	Decreased chest wall movement
Daytime fatigue	Weak cough
Morning headache	Sweating
Difficulty clearing secretions	Tachycardia
Apathy	Morning confusion, hallucinations
Poor appetite	Weight loss
Poor concentration and/or memory	Mouth dryness

Modified from Leigh *et al.* [28].

Non-invasive positive-pressure ventilation and, less frequently, invasive mechanical ventilation (IMV) are used to alleviate symptoms of respiratory insufficiency and prolong survival. There is no clear evidence regarding the timing and criteria for use of NIPPV and IMV in patients with ALS (Table 9). The use of mechanical ventilation varies between countries, reflecting economic and cultural differences [28,142]. Ideally, the patient's advance directives and a plan for management of respiratory insufficiency should be established before respiratory complications occur [28,35,142].

Table 9 Proposed criteria for NIPPV [from references 28,135,138]

Symptoms/signs related to respiratory muscle weakness. At least one of the following
Dyspnoea
Tachypnoea
Orthopnoea
Disturbed sleep due to nocturnal desaturation/arousals
Morning headache
Use of auxiliary respiratory muscles at rest
Paradoxical respiration
Daytime fatigue
Excessive daytime sleepiness (ESS > 9)
Abnormal respiratory function tests. At least one of the following
Forced vital capacity < 80% of predicted value
Sniff nasal pressure < 40 cmH_2O
PI max < 60 mmH_2O
Significant nocturnal desaturation on overnight oximetry
Morning blood gas *p*CO2 > 45 mmHg

ESS, Epworth Sleepiness Score; NIPPV, non-invasive positive-pressure ventilation.

Non-invasive positive-pressure ventilation increases survival and improves patients' quality of life and is the preferred therapy to alleviate symptoms of respiratory insufficiency [47,49,137–142] (of which [140] is Class I). Treatment is usually initiated at night to alleviate symptoms of nocturnal hypoventilation (Table 9). NIPPV improves quality of life and prolongs survival in patients presenting with respiratory insufficiency, although this has not been confirmed in patients with bulbar onset disease [140,142]. Patients with bulbar palsy are less compliant with NIPPV, due in part to increased secretions [81]. The use of diaphragmatic pacing or respiratory exercises in ALS is not established [143,144].

Invasive mechanical ventilation can prolong survival in ALS, in some cases for many years. However, no documented improvement in quality of life has been reported, and there is a risk that some patients will develop a 'locked-in' state. The availability and cultural acceptability of IMV in patients with ALS varies greatly between different countries and cultures. It is costly and has significant emotional and social impacts on patients and caregivers (Table 10) [33,48,145,146].

Parenteral morphine, a benzodiazepine and an antiemetic are used when the patient decides that ventilatory support should be withdrawn [146]. There is Class I evidence for the use of opioids and/or oxygen to treat dyspnoea in patients with terminal cancer or chronic obstructive pulmonary disease [reviewed in 147,148], but no controlled studies in ALS exist.

Improving the clearance of bronchial secretions is important in patients with ALS to promote quality of life, improve NIV tolerance and decrease the risk of infection [81]. Cough-assisting devices and chest wall oscillation may be of value [149,150].

Table 10 The advantages and drawbacks of invasive mechanical ventilation

Advantages
Increases survival time
Prevents aspiration
Ability to provide more effective ventilator pressures and better gas exchange
Drawbacks
Generates more bronchial secretions
Increases risk of infection
Introduces risk of tracheo-oesophageal fistula, tracheal stenosis or tracheomalacia
Greatly increased costs
Increased family and carer burden, including 24-h nursing requirement
Ethical issues regarding discontinuation

Recommendations

1. Symptoms or signs of respiratory insufficiency (including symptoms of nocturnal hypoventilation) should be checked at each visit (GCPP).

2. Forced vital capacity and vital capacity are the most available and practical tests for the regular monitoring of respiratory function (GCPP).

3. SNP may be used for monitoring, particularly in bulbar patients with weak lips (GCPP).

4. Percutaneous nocturnal oximetry is recommended as a screening test and for monitoring respiratory function (GCPP).

5. Symptoms or signs of respiratory insufficiency should prompt discussions with the patient and caregivers about treatment options and the terminal phase. Early discussions are needed to allow advance planning and directives (GCPP).

6. NIPPV should be considered in preference to IMV in patients with symptoms or signs of respiratory insufficiency (GCPP).

7. NIPPV can prolong survival for many months (level A) and may improve the patient's quality of life (level C).

8. Active management of secretions and provision of cough-assist devices can increase the effectiveness of assisted ventilation in ALS (GCPP).

9. IMV has a major impact upon caregivers and should be initiated only after informed discussion (GCPP).

10. Unplanned (emergency) IMV should be avoided through an early discussion of end-of-life issues, co-ordination with palliative care teams and appropriate advance directives (GCPP).

11. Oxygen therapy alone should be avoided as it may exacerbate carbon dioxide retention and oral dryness. Use oxygen only if symptomatic hypoxia is present (GCPP).

12. The medical treatment of intermittent dyspnoea should involve:
a for short dyspnoeic bouts: relieve anxiety and give lorazepam 0.5–2.5 mg sublingually;
b for longer phases of dyspnoea (> 30 min): give morphine 2.5 mg orally or s.c. (GCPP)

13. For the medical treatment of chronic dyspnoea, start with morphine 2.5 mg orally four to six times daily. For severe dyspnoea, give morphine s.c. or as an i.v. infusion. Start with 0.5 mg/h and titrate. If needed, add midazolam (2.5–5 mg) or diazepam for nocturnal symptom control and to relieve anxiety (GCPP).

Enteral nutrition in patients with ALS

Weight loss at time of diagnosis is an independent prognostic factor of survival in ALS [151]. Data indicate that patients with ALS have an increased resting energy expenditure [152]. The initial management of dysphagia is based on the following: dietary counselling, modification of food and fluid consistency (blending food, adding thickeners to liquids), prescription of high-protein and high-caloric supplements, education of the patient and carers in feeding and swallowing techniques such as supraglottic swallowing and postural changes [153,154] and flexing the neck forward on swallowing to protect the airway ('chin-tuck manoeuvre'). Some patients with difficulty swallowing tap water can more easily drink carbonated fluids and/or ice-cold liquids. When tube feeding is needed, three procedures obviate the need for major surgery and general anaesthesia: percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG, or radiologically inserted gastrostomy) and nasogastric tube (NGT) feeding.

Percutaneous endoscopic gastrostomy is the standard procedure for enteral nutrition in ALS and is widely available [153,154]. PEG improves nutrition, but there is no convincing evidence that it prevents aspiration or improves quality of life or survival [154] (Class III). The procedure requires mild sedation and is therefore more hazardous in patients with respiratory impairment and/or at an advanced stage of the disease [153,154]. Non-invasive ventilation during the PEG procedure may be feasible in patients with respiratory impairment (Class IV) [155]. The timing of PEG is mainly based on symptoms, nutritional status and respiratory function [156]. To minimize risks, PEG should be performed before vital capacity falls below 50% of predicted [154–156] (Class IV). PRG is a newer alternative to PEG and has the major advantage that it does not require patient sedation for insertion [155–158]. PRG may be as satisfactory and better tolerated than PEG [158–161], but PRG is not widely available. NGT insertion is a minor procedure that can be performed on all patients, but it can have drawbacks such as increasing oropharyngeal secretions or causing nasopharyngeal discomfort or even ulceration [162,163].

Recent studies suggest that home parenteral nutrition is possible as an alternative to enteral feeding in patients with advanced ALS and poor respiratory function [163,164] (Class IV).

Recommendations
1. Bulbar dysfunction and nutritional status, including body weight, should be checked at each visit. Difficulty drinking tap water is frequently the first sign of significant dysphagia (GCPP).
2. Patients should be referred to a dietitian as soon as dysphagia appears. A speech and language therapist can give valuable advice on swallowing techniques (GCPP).
3. The timing of PEG/PRG is based on an individual approach taking into account bulbar symptoms, malnutrition (weight loss of over 10%), respiratory function and the patient's general condition. Early insertion of a feeding tube is recommended (GCPP).
4. When PEG is indicated, patient and carers should be informed: (i) of the benefits and risks of the procedure; (ii) that it is possible to continue to take food orally as long as it is possible; and (iii) that deferring PEG to a late disease stage may increase the risk of the procedure (GCPP).
5. PRG is a suitable alternative to PEG. This procedure can be used as the procedure of choice or when PEG is deemed hazardous (GCPP).
6. Tubes with relatively large diameter (e.g. 18–22 Charrière) are recommended for both PEG and PRG to prevent tube obstruction (GCPP).
7. Prophylactic medication with antibiotics on the day of the operation may reduce the risk of infection (GCPP).
8. NGT feeding may be used in the short-term and when PEG or PRG is not suitable (GCPP).
9. Home parenteral nutrition may be used in patients with advanced ALS (GCPP).

Cognition in ALS

Amyotrophic lateral sclerosis is associated with a frontotemporal syndrome in a significant proportion of cases, and these patients have a shorter survival [165–167] (Class IV). Approximately 5–15% of patients with ALS meet the diagnostic criteria for frontotemporal dementia, typically frontal variant with executive dysfunction and behaviour change [168,169] (Class III)

although progressive aphasias have been described. A further third of patients show mild cognitive (ALSci) and/or behavioural (ALSbi) impairment [168,169]. ALSci is associated with early deficits in verbal (letter) fluency and a mild dysexecutive syndrome [170], (Class III). Language changes are sometimes reported as are symptoms of memory impairment, but these are more likely due to an encoding rather than a retention deficit [170]. ALSbi shows behaviour change that partially meets criteria for frontotemporal dementia, with apathy most commonly reported [171,172] (Class IV). Impairment in emotional and social cognition has also been described [173,174] (Class III). Cerebral atrophy on magnetic resonance imaging or ocular fixation instabilities may be biomarkers of behavioural and cognitive abnormalities [175,176] (Class III).

A number of cognitive screening batteries have been developed [177,178] (Class III), [179] (Class IV). Verbal (letter) fluency deficits are a sensitive measure of cognitive dysfunction if testing is appropriately modified for physical deficits and results standardized to educational attainment and premorbid IQ [170] (Class III).

Carers may be unaware of mild impairment as increasing physical disability results in a loss of autonomy and a greater reliance on others for daily tasks. Executive dysfunction may manifest as difficulties in managing affairs/finances, planning for the future, making decisions and learning new tasks, including the use of equipment associated with symptomatic treatment for ALS (e.g. gastrostomy, NIV).

Recommendations

1. A frontotemporal syndrome occurs in up to half of patients with ALS (level B) and is associated with a poorer prognosis. Symptoms of cognitive dysfunction may appear before or after the onset of motor symptoms.
2. The Mini-Mental State Examination is an insensitive test for ALSci and ALSbi.
3. Rapid screening tools that include tests of verbal fluency can identify patients in whom more detailed neuropsychological evaluation is mandated (level C).
4. In all patients with frontal dysexecutive syndromes, care needs to be taken to ensure informed consent during decision-making; capacity issues may need to be considered (GCPP).
5. Carers/healthcare professionals should be informed of the symptoms of dysexecutive syndrome and trained in their management (GCPP).

Communication in patients with ALS

The majority of clinically apparent communication difficulties in ALS result from dysarthria. However, subtle changes in language function may also occur, as evidenced by reduced verbal output, reduced spelling ability, increased word-finding difficulties and impaired auditory comprehension of specific classes of language (e.g. verbs more than nouns) and more complex language constructs [179–181]. Deficits may be subtle and only identifiable with formal neuropsychological testing [170,182]. Language impairment can reduce the quality of life of both patients and carers and can make clinical management difficult (Class IV) [182]. Formal neuropsychological evaluation and support may be required in patients with concomitant evolving language deficits (see previous section). The overall goal should be to optimize the effectiveness of communication, concentrating on meaningful interpersonal communication with the primary carer and family. This should include strategies for effective conversation and the introduction of alternative communication devices where appropriate.

Augmentative and alternative communication systems can substantially improve the quality of life for both patients and carers. Prosthetic treatments (palatal lift and/or a palatal augmentation prosthesis) can be useful in the reduction of hypernasality and improvement of articulation, but no formal comparative studies in ALS exist. For those requiring full mechanical ventilation, eye-pointing, eye-gaze or head-tracking augmentative high-tech communication devices may be useful.

Recommendations

1. Regular assessment (i.e. every 3–6 months) of speech and language function by a trained speech and language therapist is recommended (GCPP).
2. Those with evidence of early language deficits should undergo full neuropsychological testing (GCPP).
3. The use of appropriate communication support systems (ranging from pointing boards with figures or words, to computerized speech synthesizers) should be individualized and appropriate training and support provided as required (GCPP).

Palliative and end-of-life care

A palliative care approach should be incorporated into the care plan for patients and carers from the time of diagnosis [183]. The aim of palliative care is to maximize the quality of life of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death and supporting the family in bereavement [184]. Early referral to a specialist palliative care team is appropriate. Palliative care based in the community or through hospice contacts (e.g. home care teams) can proceed in partnership with clinic-based

neurological multidisciplinary care. A small proportion of patients with ALS express interest in assisted suicide [185] and may choose euthanasia where it is legalized [186]. Other aspects of terminal care have been covered in previous sections.

Recommendations

1. Whenever possible, offer input from a palliative care team early in the course of the disease.
2. Initiate discussions on end-of-life decisions when the patient asks or provides an opportunity for discussion on the provision of end-of-life information and/or interventions.
3. Discuss the options for respiratory support and end-of-life issues if the patient has dyspnoea, other symptoms of hypoventilation (see Table 8) or a forced vital capacity below 50%.
4. Inform the patient of the legal situation regarding advance directives and the naming of a healthcare proxy. Offer assistance in formulating an advance directive (GCPP).
5. Re-discuss the patient's preferences for life-sustaining treatments every 6 months (GCPP).
6. Initiate early referral to hospice or homecare teams well in advance of the terminal phase of ALS (GCPP).
7. Be aware of the importance of spiritual issues for the quality of life and treatment choices. Establish a liaison with local pastoral care workers to be able to address the needs of the patient and relatives (GCPP).
8. For the symptomatic treatment of dyspnoea and/or intractable pain, use opioids alone or in combination with benzodiazepines if anxiety is present. Titrating the dosages against the clinical symptoms will rarely if ever result in life-threatening respiratory depression (GCPP).
9. Terminal restlessness and confusion because of hypercapnia can be treated with neuroleptics (e.g. chlorpromazine 12.5 mg every 4–12 h p.o., i.v., or p.r.) (GCPP).
10. Use oxygen only if symptomatic hypoxia is present (GCPP).

Future developments

Being a syndrome with low incidence and short survival, most recommendations are GCPPs based on the consensus of experts in the field of ALS. Further randomized and double-blind clinical trials are urgently needed to improve the management of ALS.

Research recommendations

1. Further studies of biomarkers (imaging, blood and cerebrospinal fluid proteomics and metabolomics, neurophysiological markers) to aid earlier specific ALS diagnosis and to monitor possible effects in clinical trials.
2. Further studies of the impact of specialist MND clinics on clinical outcomes, quality of life and carer burden.
3. Further studies to optimize the symptomatic treatment of muscle cramps, drooling and bronchial secretions in patients with ALS.
4. Better criteria for defining the use of PEG, PRG, NIV and IMV.
5. Further studies to evaluate the effects of PEG/PRG, cough-assisting devices and ventilation support on quality of life and survival.
6. Further studies to evaluate language dysfunction and its treatment in ALS.
7. Systematic studies to assess cognitive impairment and the frequency of frontal lobe dysfunction in ALS and to standardize clinical, neuropsychological and neuroradiological methods in this field. Future ALS diagnostic criteria should include parameters regarding cognitive dysfunction and dementia.
8. Studies of the medico-economical impact of more expensive procedures (NIV, IMV, cough-assisting devices, advanced communication equipment).
9. Further studies to harmonize the patient databases of ALS centres.
10. Further studies on the psychosocial and spiritual determinants of quality of life in patients and their family caregivers are needed, as well as studies on the prevalence of, and determinants for, wishes for a hastened death.

Conflicts of interest

Dr. Andersen has served as a consultant for Avanir Pharmaceuticals. The other authors report no conflicts of interest.

Funding

The present guidelines were prepared without external financial support.

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