

Reviewing evidences on the management of patients with motor neuron disease

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- Objective** To review evidences on the management of patients with motor neuron disease.
- Data sources** PubMed literature searches from January 1982 up to January 2011.
- Study selection** Key words for literature search were “motor neuron disease review (MND)”. Only the articles which concentrated on the ventilation, nutrition, cognitive or multidisciplinary approaches for motor neuron disease were included. Case reports were not included in the review. In addition, publications were identified using the World Wide Web from references in these papers. Only articles in English were considered.
- Data extraction** A total of 782 articles were retrieved using the key word search, of which 72 concentrated on ventilation, nutrition, cognitive or multidisciplinary approaches. From these, 43 articles were eventually included and formed the basis of this review.
- Data synthesis** Motor neuron disease is an adult-onset neurodegenerative disease that leads to weakness of limb, bulbar, and respiratory muscles. It displays an ethnic variation in incidence; 90% of cases are sporadic and 10% are familial. New diagnostic criteria have been proposed to increase diagnostic sensitivity. Proper clinical studies, electrophysiology, and neuroimaging are necessary before reaching a diagnosis of motor neuron disease. Riluzole remains the only disease-modifying drug approved for this disease; it prolongs life by 3 to 4 months. Multidisciplinary care units are important in the management of motor neuron disease patients. Non-invasive positive pressure ventilation prolongs life in motor neuron disease patients with respiratory failure. Enteral feeding is usually recommended for affected patients with malnutrition. Cognitive impairment is common in these patients, for whom a formal neuropsychiatric assessment is recommended. Appropriate palliative care is needed for these patients in order to improve their quality of dying.
- Conclusion** Motor neuron disease is an incurable disease, for which a highly effective treatment is still pending. Symptomatic treatment remains the mainstay of management. A multidisciplinary approach embracing advances in non-invasive ventilation and gastrostomy can improve quality of life and extend the survival of motor neuron disease patients.

Key words

Amyotrophic lateral sclerosis; Motor neuron disease; Muscle weakness; Muscular atrophy; Riluzole

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Introduction

With improvements in assessment and growing awareness of motor neuron disease (MND), its reported incidence is increasing, particularly in ageing populations. This review therefore focused on evidence-based management of MND patients.

PubMed literature searches from January 1982 up to January 2011 were conducted using the key words: “motor neuron disease review (MND)”. Only the articles which concentrate on the ventilation, nutrition, cognitive or multidisciplinary approach of MND were included. Case reports were not included in the review. For articles on the same or related topics, those published at later or more recent dates were selected. Additional publications were identified using the World Wide Web from the references of these papers. Only articles in English were considered. Articles including the management

of MND were included in the review. A total of 782 articles were retrieved using the key words. Of these, 72 articles concentrated on the ventilation, nutrition, cognitive or multidisciplinary approach of MND and 43 articles were finally included and formed the basis of this review.

Epidemiology

There is an ethnic variation in the incidence of MND. In Caucasian populations, the lowest reported incidence was 0.6 per 100 000 person-years in Italy¹ and the highest was 2.4 per 100 000 person-years in Finland.² A recent study from Taiwan shows an incidence of 1.05 per 100 000/year.³ In Hong Kong, compared to worldwide figures the incidence remains low at 0.6 per 100 000 person-years, though according to one Hong Kong study a significant increase in MND or related diseases has been encountered in the last decade.⁴ This increase in incidence/prevalence in Hong Kong is likely due to the increase in average life expectancy.

Pathophysiology of motor neuron disease

Motor neuron diseases are characterised by selective degeneration of motor neurons, including the pyramidal fibres in the cerebral cortex, motor neurons in ventral horn cells, and cranial motor neurons. About 90% of cases of MND are sporadic, there being no known cause or family history. The remaining 10% of cases are familial, defined either by a family history or testing positive to a known associated genetic mutation. Thus, the *SOD1* gene mutations have been found in approximately 20% of individuals with the inherited forms of amyotrophic lateral sclerosis (ALS).⁵ The *SOD1* gene encodes for the enzyme superoxide dismutase, a free radical scavenger that reduces cellular oxidative stress throughout the body.

The most common variant of MND is ALS, in which patients demonstrate evidence of both anterior horn cell and corticospinal tract dysfunction. Progressive muscular atrophy (PMA) is a variant in which there is exclusively lower motor neuron involvement. It is slightly more common in men, has an earlier mean age of onset and a better prognosis than ALS. Another variant of MND is primary lateral sclerosis (PLS), with only upper motor neuron degeneration. Evidently, PMA and PLS account for approximately 4 and 2% of MND cases, respectively,⁶ though many of these patients progress to ALS over time.⁷

Clinical features

Development of MND ensues at different rates in different people and affects individuals in different

治理運動神經元病患者的文獻回顧

- 目的** 回顧治理運動神經元病 (MND) 患者的實證。
- 資料來源** 在醫學資料庫PubMed中搜尋由1982年1月至2011年1月發表的文獻。
- 研究選取** 用以搜索文獻的關鍵詞為「運動神經元病」(MND)。本文只回顧對於換氣、營養、認知、或以多重學科方法分析此病的研究。此外，再利用互聯網搜尋揀選文章內的參考文獻。本文只採納以英文編寫的文章，病例報告並未被納入研究範圍內。
- 資料選取** 利用關鍵詞共搜索到782篇文章，其中72篇集中討論MND的換氣、營養、認知或多重學科方法。最後從中揀選了43篇文章成為此文獻回顧的基礎。
- 資料綜合** MND是一種成人發病的神經元退化病，它會令肢體、腦橋延髓和呼吸肌肉退化。MND的發病率是有種族分別的；九成MND是自發的，另一成與遺傳有關。近年建議採用的診斷標準增加了診斷的敏感性。診斷MND時需要適當的臨床研究、電生理學研究和腦部影像技術。Riluzole仍然是目前唯一對MND有緩解作用的藥物，更有研究證實它能延長病人壽命三至四個月。多重學科的治療對MND患者很重要。非侵入性的正壓透氣有助延長呼吸衰竭的MND患者的壽命。對於營養不良的病人，通常會使用腸哺育營養。建議使用正式的神經精神學評估來確認MND患者常見的認知障礙。MND患者需要有適當的營養治療以改善終末的生命素質。
- 結論** 迄今尚無有效的方法治療MND，期待最終可以尋找出有高度療效的藥物。對症治療仍然是治理MND的主流方法。多重學科的治療與非侵入性的正壓透氣，加上腸哺育營養的發展有助改善MND患者的生活素質和延長他們的生存期。

ways. Symptoms include weakness in the arms, hands and legs, posing difficulty in achieving daily tasks. When throat muscles were affected, swallowing and speech are affected. Difficulty in breathing is experienced if the muscles of the chest wall are affected. As lower motor neurons degenerate, lower motor neuron lesion signs (muscle atrophy, fasciculations and weakness) manifest. As upper motor neurons degenerate, spastic tone, hyperreflexia and upgoing plantar reflex can be discerned. The neurological disturbance spread within and then across multiple spinal and cranial (lumbosacral, thoracic, cervical, and bulbar) segments.

Evaluation and differential diagnosis of motor neuron disease

Various laboratory, electrophysiology, and neuroimaging studies are necessary before arriving

at a diagnosis of MND. Such studies serve to exclude treatable causes. Thus, hyperthyroidism can sometimes manifest clinically with weakness, fasciculations and hyperreflexia. Serum vitamin B12 and copper level are advisable as the deficiency of either may cause combined systems degeneration of the spinal cord. Serum creatinine kinase (CK) level is usually mildly increased in MND (though only mildly); greater than 10-fold increases above the normal upper limit warrant consideration of polymyositis or inclusion body myositis. Calcium and phosphate levels need checking, if hyperparathyroidism is suspected. Serum protein electrophoresis with immunofixation is needed to rule out monoclonal gammopathy, as patients with lymphoma can sometimes present with a motor neuropathy.

Genetic testing is sometimes needed to rule out Kennedy's disease (an X-linked trinucleotide repeat disorder with expansion of polyglutamine repeats in the androgen receptor gene). It manifests as purely lower motor disorder with peri-oral fasciculations, tremor, gynaecomastia, and associated diabetes mellitus; diabetes is not commonly encountered in MND patients.

Lumbar puncture is not routinely performed in patients with typical MND presentations, but reserved for those in whom a meningeal inflammatory or infiltrative disease is suspected.

All patients with suspected MND should have nerve conduction test or electromyography (EMG) studies performed to confirm the presence of multisegmental motor axonopathy and rule out alternative diagnoses. The demonstration of multiple conduction blocks in motor nerves with the finding of preserved muscle bulk in weakened muscles strongly suggests multifocal motor neuropathy, which is an immune-mediated demyelinating motor neuropathy responsive to intravenous immunoglobulin.⁸ Benign fasciculation syndrome is another condition to be considered. Affected patients usually present

with isolated fasciculations, usually in the calf muscles. Clinically there are no lower or upper motor neuron signs seen in the involved muscles (other than fasciculations). In which case EMG only shows fasciculation but without features of chronic denervation, and CK levels are normal.

Brain or cervical spinal cord magnetic resonance imaging (MRI) may provide evidence of a tumour, syrinx, herniated cervical spinal disk, features of cervical spondylosis with cord compression and other degenerative diseases. Muscle biopsy is rarely needed in MND patients, except in those with clinical features suggestive of myopathy process and/or a high CK level (Table 1).

Diagnosis

No single test can make a definitive diagnosis of MND. The diagnosis is usually based on clinical evaluation supported by electrophysiological confirmation. Regular visits by the attending physician are often needed to appreciate progression. The revised El Escorial criteria⁹ take into account the clinical, electrophysiological, neuroimaging, laboratory, and neuropathological information (Table 2). These criteria are for clinical research only and too restrictive for use in routine clinical practice. They have also been criticised as having low sensitivity.¹⁰ Thus, in 2008, the Awaji-shima consensus recommendations (Table 3) come out to modify the revised El Escorial criteria.¹¹ These emphasise the equivalence of clinical and electrophysiological test findings in establishing neurogenic changes in body regions. The category of "Clinically Probable Laboratory-Supported ALS" is rendered redundant. Electromyography is important in establishing the presence of widespread anterior horn cell damage that is unexplained by a single nerve, root, or plexus lesion by demonstrating evidence of active denervation and re-innervation.

TABLE 1. Differential diagnosis of motor neuron disorders

Symptoms	Diagnosis
Structural lesions	Brain stem tumour/mass Spinal cord tumour/mass/vascular malformations Cervical spondylotic myelopathy
Degenerative disease	Leukodystrophies (adrenoleukodystrophy, adrenomyeloneuropathy, metachromatic leukodystrophy)
Infection	Human immunodeficiency virus myelopathy
Metabolic, nutritional	Hyperthyroidism Hyperparathyroidism Vitamin B12 deficiency Copper deficiency
Neuromuscular disorders	Myasthenia gravis Inclusion body myositis Polymyositis Lambert-Eaton syndrome

TABLE 2. Revised El Escorial research diagnostic criteria for amyotrophic lateral sclerosis⁹

ALS	Criteria
Clinically definite ALS	UMN and LMN signs in three regions
Clinically definite ALS — laboratory supported	UMN and/or LMN signs in one region and the patient is a carrier of a pathogenic gene mutation
Clinically probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Clinically probable ALS — laboratory supported	UMN signs in one or more regions and LMN signs defined by EMG in at least two regions
Clinically possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs

* ALS denotes amyotrophic lateral sclerosis, UMN upper motor neuron, LMN lower motor neuron, and EMG electromyography

TABLE 3. Awaji-shima consensus recommendations for the application of electrophysiological tests to the diagnosis of amyotrophic lateral sclerosis⁸

ALS	Definition
Clinically definite ALS	Defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions
Clinically probable ALS	Defined by clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
Clinically possible ALS	Defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have to be performed and other diagnoses must have been excluded

* ALS denotes amyotrophic lateral sclerosis, UMN upper motor neuron, and LMN lower motor neuron

Disease course and prognostic markers

A previous review has shown that in MND patients, the median survival time from onset to death ranged from 20 to 48 months, only 10 to 20% survived longer than 10 years.¹² Several poor prognostic factors for survival have been proposed. Onset with the bulbar form of MND correlated with a more rapid neurological impairment but not for the time to tracheostomy.¹³ Advanced age at symptom onset, lower-than-predicted forced vital capacity (FVC) at diagnosis, long delay from symptom onset to diagnosis, low body mass index (BMI) of <18.5, and psychological distress are all associated with a poor prognosis.¹²

Neuroprotective treatment

Riluzole, a glutamate release antagonist, is the only disease-modifying drug approved for treating MND. According to two clinical trials and meta-analysis, it prolongs survival by about 3 months after 18 months of treatment.^{14,15} Riluzole may have little effect in advanced ALS and it is unclear as to when treatment should be terminated. Patients can usually tolerate riluzole with few side-effects except fatigue and nausea. Liver function needs to be regularly monitored; the treatment should cease if liver enzymes exceed 5 times the upper limit of normal or the patient develops neutropenia. Adjunctive nutritional supplements (vitamins and antioxidants) in addition to riluzole are beneficial to MND patients.¹⁶

Symptomatic treatment

In view of the limited role of drugs in prolonging survival of MND patients, symptomatic therapy has an important part in management of MND. Effective management can maximise function, improve quality of life, and increase independence. Most of the drugs used for symptomatic treatment are based on small studies, or on experience in other neurological disorders.

Respiratory issues in patients with motor neuron disease

Respiratory insufficiency in MND patients is mainly caused by respiratory or bulbar muscle weakness and can be aggravated by aspiration and bronchopneumonia, and is also responsible for the majority of deaths.¹⁷ Early recognition of dyspnoea and hypoventilation are important, as mechanical ventilation can be initiated as early as possible, which has been shown to prolong survival in MND patients.¹⁸

For the early assessment of respiratory symptoms, spirometer is usually preferred to performing lung function test. It is readily available and easy to perform. Forced vital capacity is the most commonly used parameter to assessing patients with neuromuscular disease, and was shown to be a significant predictor of survival in MND.¹⁹ A decrease in vital capacity to 50% predicted associated with respiratory symptoms.²⁰ The FVC can also be checked lying or standing; a >25% decrease in the supine

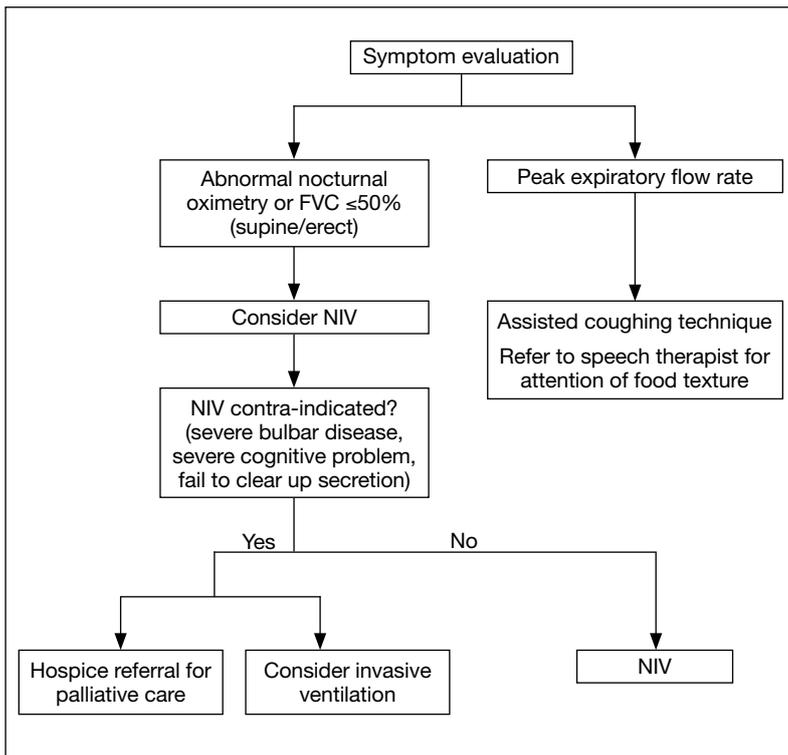


FIG 1. Algorithm on respiratory management in patients with motor neuron disease
FVC denotes forced vital capacity, and NIV non-invasive ventilation

posture suggests diaphragmatic weakness.²¹ Its disadvantages are its dependence on patient effort and co-operation as well as an adequate mouth-seal. Moreover it is insensitive for detecting problems due to significant bulbar dysfunction in the early and later stages of MND.

Hypoventilation can be reflected by elevated blood carbon dioxide and bicarbonate levels, secondary to respiratory acidosis. However, these are usually late findings. Sleep studies with overnight oximetry can reveal nocturnal desaturation. A full polysomnography is sometimes required to differentiate obstruction sleep apnoea from hypoventilation as the cause of desaturation.

In MND patients, secretions in the upper and lower airways are difficult to handle, and there is an increased risk of aspiration. Patients and carers are encouraged to learn the technique of assisting expiratory movements; using a manually assisted cough is effective for sputum clearance.²² Portable home suction is also useful for clearing the accumulated saliva in the mouth. There is no controlled study on medication with mucolytics.²³ Alteration in food texture may also help reduce the risk of aspiration.²⁴ Antibiotic should only be used if there is evidence of pulmonary infection.²⁴

In patients with MND, non-invasive ventilation (NIV) is usually considered before invasive

ventilation via tracheostomy. It has been shown to be more cost effective as it does not require nurses to help with regular home care.²⁵ It improves quality of life, prolongs survival, and reduces the rate of FVC decline, except in patients with poor bulbar function.²⁶

No prospective trial has evaluated the indications for initiating NIV; information is drawn from observational studies only. Intervention is usually recommended if respiratory symptoms develop or when the FVC is less than 50% predicted.^{27,28} Patients with cognitive problems, moderate-to-severe bulbar disease or failure to clear secretions should be considered for invasive ventilation instead.²⁹ Before the initiation of invasive ventilation, patients and caregivers should fully understand the associated ethical considerations and costs of this form of treatment. It requires frequent tracheal suctioning and a multidisciplinary team care, which includes psychological support for home ventilation.³⁰ A summary of respiratory management in MND patients is shown in Figure 1.

Nutritional issues in patients with motor neuron disease

Bulbar weakness in MND is the result of deterioration of neurons in the motor cortex and the brainstem, and clinically manifests as difficulties with mastication and dysphagia. In fact, nutrition is an independent prognostic factor for survival.³¹ Malnourished MND patients are prone to respiratory decompensation and worsening of quality of life. All MND patients need to be regularly assessed by speech therapists, lest they are prone to choking and aspiration.³² Video fluoroscopic swallowing study is useful in assessing the risk of aspiration.³³

Enteral feeding by means of percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy (RIG) is usually considered, if the patient is not fit for oral feeding, though there is no evidence to show that it can prolong survival or improve quality of life. However, enteral nutrition administered via PEG is effective in stabilising body weight/BMI.³⁴ There is no consensus on the specific timing for introducing such feeding, but dysphagia, accelerated weight loss, and low BMI are usually the key indicators.²² The American Academy of Neurology ALS Practice Parameter recommends that the PEG procedure should be carried out when the FVC is above 50% predicted, so as to minimise the risk of respiratory complications.⁸ Concerning RIG, it has the benefit of not entailing sedation, being suitable for patients with severe respiratory impairment and is safer than PEG.³⁵ Thus far, there is no guideline on the lowest limit of the FVC for safely proceeding with RIG feeding. A summary of nutrition management in MND patients is shown in Figure 2.

Sialorrhoea

Sialorrhoea is a socially disabling symptom, which also increases the chance of aspiration due to impaired handling of saliva. It is usually treatable. Amitriptyline is commonly used but patients need to be monitored for possible anticholinergic side-effects. Oral doses of not more than 50 mg twice to three times daily are usually sufficient. Botulinum toxin type A (another anticholinergic) can also be used by injection into the salivary glands, and works by reducing saliva production. However, the effect fades after several months and repeat injections are necessary. There is also a concern of the weakening effect of the drug, being administered to a patient with already-compromised swallowing and breathing. In one trial, amitriptyline and botulinum toxin were demonstrated to be equally effective.³⁶ For medically refractory sialorrhoea, low-dose palliative radiation therapy to the parotid and submandibular glands can also be tried to reduce salivary production, but side-effects include erythema, sore throat, and nausea.³⁷

Pseudobulbar emotional lability

Pseudobulbar affect in MND includes excessive laughing, crying as well as involuntary emotional expression disorder. It is estimated to affect 20 to 50% of MND patients, especially those with pseudobulbar palsy.³⁸ A fixed dose of combination of dextromethorphan and quinine is the only drug regimen shown to reduce the severity/extent of laughing and crying.³⁹ It is, however, not yet approved by the US Food and Drug Administration and has side-effects of dizziness, nausea, and somnolence.

Spasticity and cramps

Spasticity and cramps can cause pain and impair function in patients with MND. Current treatment options include stretching exercises, hydrotherapy in heated pools and pharmacotherapy (oral baclofen); gabapentin, vitamin and riluzole appear ineffective. Quinine is a popular drug used to combat cramps. However a recent review of cramp therapy in general population by an American Academy of Neurology subcommittee reported that though quinine derivatives are likely to be effective, they have significant toxicity and are best avoided for routine treatment.⁴⁰ An open-label study showed that levetiracetam is effective in the treatment of cramps and spasticity in MND patients.⁴¹ Intrathecal baclofen is usually reserved for patients refractory to other therapies and is based on a single case-control study only.

Pain

Pain is common in MND patients, for which non-

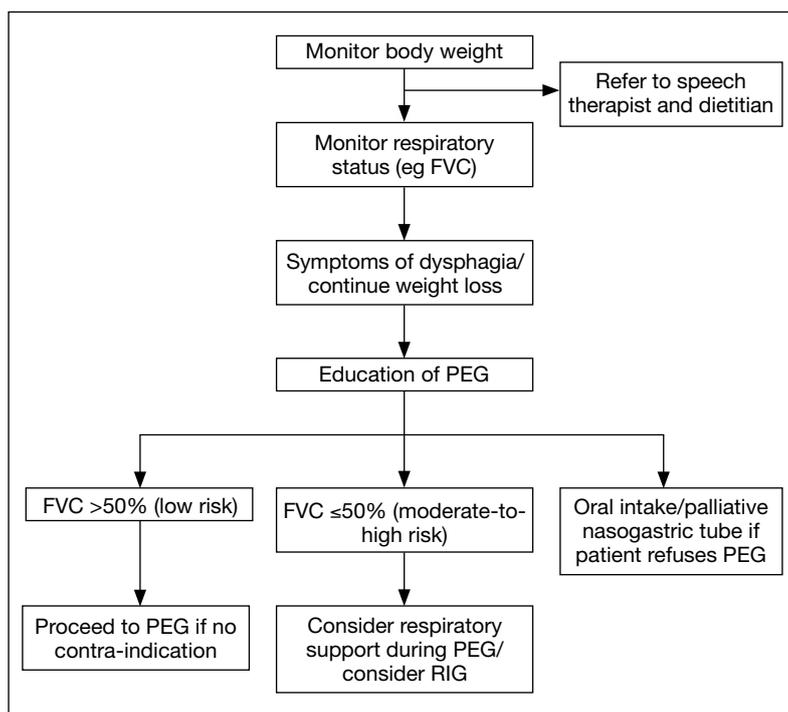


FIG 2. Algorithm on nutrition management in patients with motor neuron disease. FVC denotes forced vital capacity, PEG percutaneous endoscopic gastrostomy, and RIG radiologically inserted gastrostomy

specific pain killers are used. Treatment usually begins with simple analgesics, if followed by weak opioids (tramadol) and if needed strong opioids (morphine). Opioid side-effects, such as constipation, needed to be borne in mind.

Cognitive and behavioural impairment in patients with motor neuron disease

There is no controlled trial of treatment for depression in MND. Commonly used antidepressants include tricyclics (eg amitriptyline) and selective serotonin reuptake inhibitors (fluoxetine). For insomnia, amitriptyline and zolpidem are most often used. Benzodiazepines such as diazepam and lorazepam are common anxiolytics used in MND patients with anxiety.

Although the degenerative pathology of MND predominantly affects the motor system, cognitive and behavioural symptoms have been described for a long time. One of the largest studies of MND found 47% of such patients had cognitive impairment.⁴² A recent meta-analysis of cognitive function in MND patients based on Mini-Mental State Examinations found that immediate verbal memory, visual memory, and fluency were mostly affected.⁴³ There is currently no consensus on pharmacological treatment for cognitive or behavioural impairment in MND and no study on this issue has been published. Screening of MND patients for co-morbid conditions at diagnosis

and at regular intervals is recommended by the American Academy of Neurology Practice Parameter.²⁶

Multidisciplinary management of motor neuron disease

Multidisciplinary care units which deal with the physical, emotional, relational, and spiritual spectrum are believed to be beneficial for MND patients. Such care usually comprises several team members, including neurologist, nurse specialist, occupational therapist, physical therapist, respiratory therapist, neuropsychologist, and a social worker. Studies have shown that patients attending multidisciplinary care units survive longer and enjoy better quality of life compared to those attending merely a multidisciplinary clinic.⁴⁴ This may be related to a higher rate of riluzole use, PEG, NIV, and a fewer hospital admissions.

Palliative and end-of-life issue

Due to the progressive nature of the disease,

all MND patients eventually reach the stage of respiratory insufficiency, inadequate nutrition, and psychological distress. Appropriate palliative care should be provided to improve the quality of dying and death. The aim is to maximise patient's quality of life and that of families, by relieving symptoms as well as providing emotional and psychological support. In the US and most of the European countries, patients have the right to maintain autonomy in the terminal phase and in end-of-life decisions. However there is no specific legislation in Hong Kong to allow patients to decide on their end-of-life issues. Despite that, patient autonomy should be respected at all times during the course of the disease.

Conclusion

Motor neuron disease is incurable; no highly effective treatment is available at this stage. Symptomatic treatment remains the mainstay of management. A multidisciplinary approach coupled with the advances in NIV and gastrostomy can improve quality of life and extend the survival of such patients.

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