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MULTIDISCIPLINARY CARE IN MOTOR NEURON DISEASE

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ABSTRACT

Motor neuron disease (MND) is a progressive degenerative disorder of the motor neurons, resulting in progressive limb, bulbar and respiratory muscle weakness. No definitive disease modifying treatment is available at this time. The mainstay of management remains multidisciplinary care, which has shown to improve quality of life, prevents complications and may also increase life span.
In this review, different medical specialties necessary to offer complete multidisciplinary care are discussed. Symptomatic management of individual symptoms commonly experienced by patients with MND is elaborated on.

KEYWORDS: Motor neuron disease, multidisciplinary clinic, nutrition, respiratory support, speech

INTRODUCTION: Despite recent advances in the availability of approved drugs for the treatment of motor neuron disease (MND)/Amyotrophic lateral sclerosis (ALS), symptomatic treatment remains the main stay for the management of these patients.(1) MND can present with asymmetric or symmetric limb weakness or can have its onset in the bulbar muscles with speech and swallowing difficulties. This is a progressive degenerative disorder of motor neurons residing in the motor cortex, brain stem and anterior horns. Presenting symptoms and progression of the disease varies amongst individuals, possibly influenced by genetic and environmental factors. The median survival, from symptom onset to death, ranges from 20 to 48 months. (2) Only 10% patients with ALS live over 10 years of disease duration. (2) Older age and bulbar symptoms at onset are poor prognostic factors. (2) Overtime it has become clear that MND is not just a disorder of motor neuron degeneration but involves other brain regions too. For example, patients suffer from behavioral and cognitive issues at some point during their illness as a result of degeneration of the frontal lobes.(3) Therefore management of MND needs a holistic multi-disciplinary approach.
Multidisciplinary care of patients with MND has shown to improve quality of life, decrease complications and hospitalizations, prolong survival and decrease mortality.(1, 4-6) This review aims to describe the components necessary for successful multidisciplinary management of patients with MND and the evidence behind timely supportive interventions.

MULTIDISCIPLINARY CLINICS

Successful multidisciplinary care of MND/ALS requires specialized clinics where a patient is systematically evaluated by multiple specialists on the same day. A multidisciplinary clinic (MDC) decreases the burden on patients and care givers who would otherwise be compelled to go to different specialists, at different locations and times. A MDC provides co-ordinated care and typically includes assessment and management by multiple team members. (7, 8) At the end of the clinic, ideally, the team discusses individual specialty recommendations and comes up with a health care plan for the patient. Each team member has defined goals: (7, 8)
1. Neurologist: responsible for diagnosis, breaking the news, clinical monitoring, prescribing medications, co-ordination with other health care personnel, discussing scientific evidence, answering questions and provide information about enrollment in clinical trials. It is useful to assess the patient based on a scale such as

the ALS functional rating scale- revised (ALSFRS-R) to document the disease course.

2. Speech and language therapist: evaluates oral motor and swallowing function, gives advice for oropharyngeal exercises, is responsible for early detection of dysphagia and works with the patients on developing long term strategies for communication.

3. Nutritionist: monitors body mass index (BMI), caloric intake and provides the patient and family with a dietary plan to follow. They work in close association with the speech therapist for appropriate dietary advice according to the swallowing status. Maintaining BMI is important as rapid weight loss is considered a poor prognostic factor.

4. Physiotherapist (PT): assess mobility, physical strength and devise a home care exercise plan.

5. Occupational therapist (OT): works in association with the PT and assess home safety and performance of activities of daily living. PT and OT together assess and advice for the need of assistive devices to help with daily activities.

6. Neuropsychologist/psychiatrist: responsible for early detection of mood, behavioral and cognitive changes, helps with end of life decisions and provides emotional support for the patient and family.

7. The nurse manager and social worker works as a liaison between the patient and health care team.

The team works in close contact with a palliative care specialist, gastroenterologist and pulmonologist for timely intervention with percutaneous gastrostomy (PEG) and/or non-invasive ventilation (NIV) respectively.

Multidisciplinary care in motor neuron disease (MND)

SYMPTOMATIC MANAGEMENT

Besides disease modifying agents, specifically Riluzole (9)and possibly Edaravone(10), the mainstay of management for all MND patients remains optimal care for evolving symptoms. The aim is to improve quality of life of the patient and family, prevent complications and decrease hospitalizations.

RESPIRATORY SUPPORT

Just like other skeletal muscles, respiratory muscles also become progressively weak in MND. Inspiration is an active process, requiring contraction of intercostal, diaphragmatic and accessory muscles to generate a negative intrathoracic pressure and allow air inflow. (11) Upper motor neurons further control and modify the pattern of breathing. As a result of progressive weakness of respiratory muscles and loss of upper motor neurons, patients experience symptoms such as shortness of breath on exertion, orthopnoea, non-refreshing sleep, morning headaches and loss of appetite. Even asymptomatic patients can have respiratory muscle weakness (12), making regular screening of these patients all the more important, even in early stages of the disease. Neuromuscular respiratory failure is the most common cause of death in patients with MND/ALS. (11, 18)

In a landmark randomized control trial conducted by Bourke et al (13), non-invasive ventilations (NIV) significantly improved quality of life and survival in patients with non-bulbar ALS. Similar survival benefits were not seen in patients with bulbar symptoms; however there was improvement in sleep related symptoms in this group. (13) A recent Cochrane review (14) corroborated these findings with some suggestion that patients who have not yet developed respiratory symptoms or have mild respiratory muscle involvement may have a higher survival benefit and improvement in quality of life, however this is still under investigation.(14) NIV works by improving oxygenation, decreasing work of breathing and fatigue, improving lung compliance and reversing hypercapnia thereby improving central respiratory drive. (11) NIV should be offered to patients in a timely manner, before they develop frank respiratory failure in order to obtain the maximum quality of life and prolong survival. Assessment of respiratory function through symptoms, oxygen saturation, forced vital capacity (FVC) and maximal inspiratory pressure (MIP) is recommended at the time of diagnosis and at every 3 months follow up. Nocturnal oximetry should be considered in doubtful cases. The predicted FVC and a decline in FVC is the most important predictor of survival. (19) Ideally FVC

should be recorded both sitting and supine and a 25% drop in FVC in the supine position strongly suggests diaphragmatic weakness.(1) Patients who full fill the criteria of neuromuscular respiratory failure i.e., those with orthopnea, MIP < -60cm, FVC <50% predicted or abnormal nocturnal oximetry require NIV. (1)

The most common setting of NIV used is bi-level positive airway pressure (BIPAP). Compliance and tolerance to NIV can be an issue. Individuals with bulbar onset MND may experience difficulty in tolerating BIPAP due to pooling of secretions and weak cough, which in turn can result in a lot of anxiety.(15) Those with cognitive decline or frontotemporal dementia may show low adherence to the use of NIV.(15) Therefore a mutual decision needs to be made after extensive counseling of the patient and family. Intensive educational training has shown to improve compliance and adaptation to NIV.(16) Transtracheal invasive ventilation is offered to patients who wish to stay on long term ventilatory support, however it is resource intensive.

Diaphragmatic pacing in ALS patients was shown to decrease survival and is not recommended for MND patients at this time while further studies on this are ongoing. (17)

Along with respiratory decline, a weak cough and the consequent difficulty in clearing respiratory secretions is a common cause of lower respiratory tract infections. These patients need intensive respiratory therapy with suctioning and clearance of secretions. Mucolytic agents such as carbocisteine may be used.

HYPERSIALORRHEA

Difficulty in swallowing can give rise to build-up of saliva in the mouth, which can be socially embarrassing for the patient and can also increase the risk of aspiration pneumonia. Oral medications are tried as first line therapy. Options include amitriptyline, benztropine, trihexyphenidyl, scopolamine, atropine drops or glycopyrolate.(7, 18) If medications are unable to control the hypersialorrhea or side effects limit their use, then botox injections in the parotid and/or submandibular gland or low dose radiation to the salivary glands can be considered.(7, 18, 19)

NUTRITION

Rapid decline in weight and BMI (<18.5) is associated with progression of disease and decrease in survival.(1, 20, 21) Reasons for inadequate oral intake are multifactorial and include dysphagia, weakness of upper limbs making patients dependent on others for feeding, depression or cognitive decline and increase in the resting metabolism.(1, 20) BMI and the nutritional plan need to be documented and discussed on every visit.

Initial intervention for dysphagia can include altering consistency and texture of food and additional supplements to improve caloric intake. Ultimately, to maintain BMI, a gastrostomy is needed. A swallowing assessment performed at every visit by the speech therapist can help guide the clinician in timing discussions with the patient and family for gastrostomy placement. Feeding via gastrostomy aims to decrease the risk of aspiration, reduce the need for hospitalization and maintain body weight. (1, 22) The ideal time for gastrostomy placement is not known, however should be considered when there is more than 10% weight loss (23). The ProGas trial (22) was the first multicenter cohort study to indicate the benefits of early gastrostomy. Patients who had more than 10% loss of weight prior to PEG placement, from the time of diagnosis to the procedure, had shorter survival and were less likely to regain that weight. The risk of complications during the gastrostomy procedure is low if the FVC is ≥ 38% of predicted and the PaCo2 is normal.(24) Different methods of gastrostomy (percutaneous endoscopic, radiologically inserted or per-oral image guided) are not superior to each other and the decision is made based on the respiratory status of the patient, ability to lie flat and physician preference. (22, 25)

There have been numerous studies with insufficient evidence for the use of vitamin supplements including Vitamins A, B-complex, D, C, L-carnitine, co-enzyme Q10 and creatine monohydrate.(1, 18) Similarly, the benefits of high carbohydrate, high protein or high fat diets are controversial.(18, 20) The nutritionist should make a diet plan based on individual needs and offer high energy supplements early if necessary.

PSEUDOBULBAR AFFECT (EMOTIONAL LABILITY)

Pseudobulbar affect (PBA) refers to episodic, involuntary, excessive crying, laughter, yawning that is seen in up to 50% of MND/ALS patients.(26) This significantly impairs quality of life and effects social functioning. Antidepressants such as tricyclic antidepressants (amitriptyline) and serotonin re-uptake inhibitors (citalopram) are frequently used. (7, 20) Pioro et al reported a combination of dextromethorphan (DM) 30mg and quinidine (Q) 10mg reduced the frequency and severity of laughing and crying behaviors compared to either drug alone.(27)A fixed dose combination of DM/Q (30mg/10mg) is recommended for treatment of PBA. (7)

COMMUNICATION

The speech and language therapist guides the patient and family in exercises and to use tools to help with communication. Based on availability, assistive devices are prescribed. These include word, alphabet, sound and visual command cards, typing devices, speaker phones, sound synthesizers or personal digital assistance (PDA).

ASSISTIVE DEVICES AND EQUIPMENT

Regular assessment by the physiotherapists and occupational therapists will address the need for aids for mobility and activities of daily living (ADL). The home environment needs to be assessed for safety and adapted according to individual person's needs. For example, adjustments in bathrooms with arm rails by the toilet, elevated toilet seat, shower seat and shower bars. Devices most often used for mobility include a cane, walker, wheelchair and ankle brace for ambulation.(28) For severely weak patients a sliding transfer board at home is recommended. ADLs can be made easy by simple interventions such as modified eating utensils with thick handles for better grip, wrist braces, slip-on shoes, and electric seating controls for a beds or wheelchairs. (28) Although the cost of some of this equipment is high, there are no studies on cost effectiveness as yet. In the long run, complications of falls and immobility can be avoided, decreasing hospitalization and improving quality of life.

CRAMPS AND SPASTICITY

There is no clear evidence of benefit of a specific drug for cramps in MND patients, but quinine, gabapentin and vitamin E are widely used. (7, 29) Spasticity is treated by encouraging physical therapy and use of drugs used for increased tone in other central nervous disorders such as baclofen, tizanidine and benzodiazepines.

COGNITIVE AND MOOD IMPAIRMENT

Cognitive impairment is seen in up to 30% ALS patients, mostly behavioral variant of frontotemporal dementia.(30) Cognitive deficits in fluency, language, social cognition, executive functions and verbal memory have been documented. (31) The role of the neuropsychiatrist/psychologist in the MDC is to assess all MND patients using neuropsychological testing. Early intervention and counseling for cognitive and behavioral changes will improve quality of life and decrease care giver burden.

Depression and/or anxiety may result from uncertainty or delay in diagnosis, prognosis of the disease, as part of the cognitive changes or due to drug side effects. All patients are screened for mood disorders and treated accordingly. No drugs are indicated for mood disorders specifically in MND; however they can be prescribed based on their side effect profile, which may even help other symptoms e.g hypersialorrhea and PBA.

INSOMNIA AND FATIGUE

Insomnia and fatigue become common complaints in MND especially as the disease progresses. Multiple aspects of the disease already discussed contribute to sleep disturbances. The earliest sign of respiratory muscle weakness may just be insomnia that is related to nocturnal hypoventilation.(15) Other factors affecting sleep include depression, anxiety, immobility, muscle cramps and restless legs syndrome.(15) Decrease in restful sleep, in turn, can aggravate other symptoms like depression, anxiety, cramps and cognitive decline. Clinically, insomnia is treated with medications such as zolpidem and amitriptyline while identifying the primary cause and its treatment. Modafinil may be used for excessive day time somnolence or fatigue.(20)

DISEASE MODIFYING THERAPIES

Riluzole is the first drug shown to have some benefits in patients with ALS and was approved by the FDA in 1995. It's mechanism of action is not clearly known but it has shown to modulate the effects of glutamate, both by inhibiting its release and modulating post synaptic glutamate receptor signaling. Riluzole is also reported to have neuroprotective effects. (32) It slows progression of disease and lengthens survival by at least 3 months, initially shown in two large placebo controlled trials.(9, 33) It is safe to use at a dose of 100mg daily, with the most common side effects of raised liver enzymes, asthenia, dizziness and gastrointestinal discomfort.(33) Riluzole must be offered to all patients with a diagnosis of MND/ALS.

Hope came with the discovery of a free radical scavenger, Edaravone, which was first approved in Japan in 2015 for treatment of ALS, followed by FDA approval in 2017.However, it is not yet approved in Europe, and there are widespread conflicting opinions amongst neuromuscular specialists about its benefits and accelerated approval. Edaravone is delivered by intravenous infusions in cycles consisting of daily dosing for 2 weeks followed by a 2-week drug-free period .The initial trial conducted in Japan had a short 6 months duration of intervention with very constrictive

inclusion criteria. These criteria included age 20 to 75 years, a Japan ALS Severity Classification of grade 1 or 2 (no to mild disability), scores of at least 2 points on all 12 items of the ALS Functional Rating Scale-Revised (ALSFRS-R), forced vital capacity of 80% or more, definite or probable ALS according to the revised El Escorial criteria and disease duration of 2 years or less.(10) The proportion of patients with bulbar onset ALS was less and those with score of 3 or less on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency were excluded. The results showed a slowing in the decline of the ALSFRS-R score by 33% over the 6 months period. Although the positive outcome is remarkable, this needs further trials, with inclusion of a wider spectrum of MND patients, longer duration of treatment and follow up for long term benefits and side effects.

New treatments are under investigation. Ongoing trials are looking at the effect of stem cell and gene therapies targeting Superoxide dismutase 1 (SOD 1) and C9orf2 repeat expansions seen in some cases of ALS.(34)

CONCLUSION

In a disease where patients and families easily give up hope due to lack of definitive treatment, it is necessary for the treating physician to explain the importance and impact of multidisciplinary care. MDC remains the standard of care for management of MND to improve the quality of life, minimize hospitalizations and improve health outcomes.(35) Palliative care and end of life care is also an integral part of the multidisciplinary care. The MDC team will assist the patient and family with an end of life care plan to avoid anxiety and emotional decisions, when the time comes. In our experience, MDC makes acceptance of the disease easier both for patients and their caregivers. It not only serves to address every aspect of the disease but at times can also serve as a support group for patients and families attending the clinic.

Establishing and running a MDC is expensive and often the cost is supported by individuals or philanthropic organizations (35), however this is the only proven way to improve the quality of life of patients with MND and can also serve as resource for research. As the search for a disease modifying treatment continues, committing resources and personnel to MDCs for the management of motor neuron disease should remain a priority for tertiary care neurological centers.

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