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Chapter I

MOTOR NEURON DISEASE: CAUSES, CLASSIFICATION AND TREATMENTS

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ABSTRACT

Motor Neuron Disease (MND) is the most common chronic neurodegenerative disorder of the motor system in adults. It is a relatively rare disease with a reported population incidence of between 1.5 and 2.5 per 100,000 per year worldwide. The only established risk factors are age and family history, with age being the most important factor. The disease occurs throughout adult life, with the peak incidence between 50 to 75 years of age. MND occurs more commonly in men than in women in a ratio of 3:2. MND is characterized by the loss of motor neurons in the cortex, brain stem, and spinal cord, manifested by upper and lower motor neuron signs and symptoms affecting bulbar, limb, and respiratory muscles. Death usually results from respiratory failure and follows on average two to four years after onset, but some may survive for a decade or more.

Whilst the aetiology of MND is unknown, current evidence suggests that multiple interacting factors contribute to motor neuron injury in MND. The working hypothesis is that MND, like many other chronic diseases, is a complex genetic condition and the relative contribution of individual environmental and genetic factors is likely to be small. The three key pathogenetic hypotheses are genetic factors, oxidative stress and glutamatergic toxicity, which result in damage to critical target proteins such as neurofilaments and organelles such as mitochondria.

The symptoms in MND are diverse and challenging and include weakness, spasticity, limitations in mobility and activities of daily living, communication deficits and dysphagia, and in those with bulbar involvement, respiratory compromise, fatigue and sleep disorders, pain and psychosocial distress. Hence, the burden of disease and

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economic impact of MND upon patients, their caregivers (often family members) and on society is substantial, often beginning long before the actual diagnosis is made, and increasing with increasing disability and the need for medical equipment and assisted care.

At present, the only approved drug treatment for MND in the USA, Australia and in many European countries is riluzole, which is thought to prolong median survival by about two to three months. In the absence of a cure or indeed any medical intervention, which might stop the progression of MND, the management relies mostly on symptomatic, rehabilitative and palliative therapy, which is the focus of this chapter. An update in the symptomatic and disability management of MND is provided, covering the interface between neurology, rehabilitation and palliative care and incorporates issues encountered over the spectrum of disease, including activity and pain related issues, respiratory and dysphagia issues and psychosocial changes. Recent trends, developments and future research in rehabilitation approaches that maintain and restore functional independence and quality of life will be presented.

1.1. INTRODUCTION

Motor neuron disease (MND), also commonly known as amyotrophic lateral sclerosis (ALS), is a chronic neurodegenerative disorder of the motor system in adults, characterized by the loss of motor neurons in the cortex, brain stem, and spinal cord, manifested by progressive upper and lower motor neuron signs and symptoms affecting bulbar, limb, and respiratory muscles [1]. It was first described by Charcot in the nineteenth century [2] and is also known by the eponym "Lou Gehrig's Disease", after the famous baseball player who was affected with the disease. Death usually results from respiratory failure and follows on average two to four years after onset, but some may survive for a decade or more [3].

MND is a relatively rare disease with a reported population incidence of between 1.5 and 2.5 per 100,000 per year [4] and a prevalence of 2.7-7.4 per 100,000 population [5]. Age is the most important risk factor and the disease occurs throughout adult life, with the peak incidence between 50 to 75 years of age [6]. MND occurs more commonly in men than in women in a ratio of 3:2 [7].

MND is lifelong and persons with MND (pwMND) live with a range of problems that affect every day functional activities. The International Classification of Functioning, Health and Disability (ICF) [8], defines a common language for describing the impact of disease at different levels: impairment (body structure and function), limitation in activity and participation.

Within this framework MND related impairments (weakness, spasticity), can limit 'activity' or function (decreased mobility, self-care, pain) and 'participation' (driving, employment, family, social reintegration). 'Contextual factors', such as environmental (extrinsic) and personal factors (intrinsic) have an impact on the pwMND, their families and the society. MND therefore has personal costs such as reduced quality of life (QoL) and also significant economic costs which may result from increased demand for health care, social services, and caregiver burden.

1.2. IMPACT OF MND

The burden of disease and economic impact of MND upon patients, their caregivers (often family members) and on society is substantial, often beginning long before the actual diagnosis is made, and increasing with increasing disability and the need for medical equipment and assisted care [9]. It has been estimated that basic patient equipment costs (including hospital bed, electric wheelchair, augmentative communication equipment) can cost over USD$40,000 whilst mechanical ventilation costs roughly USD$200,000 a year [9]. These costs do not include earnings loss, therapy costs, and formal and informal care, which often make up the bulk of costs but are often not calculated. Within the Australian healthcare system, provision of care in people with terminal illness largely falls onto informal, unpaid caregivers, usually family and/or friends [10]. In a recent study of Australian pwMND in the community (n=44) [11], 1/3 required help 2-3 times a day for personal care whilst 1/3 required the presence of someone most of the time. A quarter of these 44 pwMND received assistance solely from family. It is therefore not surprising that primary caregivers have been estimated to spend a mean of 9.5 hours a day caring for patients even where there is paid assistance [12]. Whilst the informal care costs for pwMND in the community (by families and others) is not known, these costs account for 43% of total costs in other neurodegenerative conditions [13] (where disability is less marked, such as in multiple sclerosis) and is likely to be as substantial if not more, in MND. Finally, it is well documented that a huge proportion of health care dollars are spent in the last 30 days of a person's life [14]. This is particularly pertinent in a rapidly fatal condition such as MND.

1.3. EPIDEMIOLOGY AND RISK FACTORS

The collection of epidemiological data is challenging due to the low incidence rates of MND. However, the establishment of a number of population-based registers worldwide (mainly in Europe and Australia), has enabled a clearer understanding of MND epidemiology. The incidence and mortality rates of MND have slowly increased over decades [15,16], likely at least partly due to longer life expectancy [17] with improved medical management and supportive care. Incidence rates range between 1.5 and 2.5 per 100,000 per year [4]; whilst prevalence rates range between 2.7-7.4 per 100,000 population [5] which equates to roughly 25,000 in North America [18], 5000 in the UK [19] and 1200 in Australia [20]. The incidence may be higher in Caucasians than in other ethnic groups (African, Asian, Hispanic) but this has been difficult to determine due to methodology variations in studies of non-Caucasian populations [21].

Age and family history are the only well-established risk factors for MND. There is class II evidence that smoking is also a risk factor [22]. Evidence for other risk factors such as physical activity and exposure to heavy metals is conflicting [23-25].

Geographically, the cluster of "Western Pacific ALS" during the 20th century in Guam, the Kii peninsula of Japan and Papua New Guinea has suggested an environmental contribution to MND pathogenesis. However, whilst a number of hypotheses have been proposed, including the dietary consumption of cycad (Cycas circinalis) [26], no definitive cause has been found [27].

The role of genetics is important in MND. Familial MND, more commonly referred to as familial ALS (FALS), accounts for 10% of MND whilst a number of genetic loci have been found to be associated with idiopathic MND (remaining 90%) suggesting genetic susceptibility in pathogenesis [28-30]. At least fifteen chromosomal loci have been linked with familial MND. Familial MND is phenotypically and genetically heterogenous. Majority of familial MND are autosomal dominant in nature and 20% are linked to FALS type 1 or the superoxide dismutase (SOD1) gene [31]. Other autosomal dominant familial MND include FALS types 3 [32], 5 [33], 6 (FUS gene) [34,35], 7 [36], 8 [37], 9 (ANG gene) [38], 10 (TARDBP gene) [39], 11 (FIG4 gene) [40], NF-H gene [41], DAO gene [42], X-linked [43] and MND with FTD [44]. Autosomal recessive familial MND includes FALS 2 [45] and 5 [46].

1.4. AETIOLOGY AND PATHOGENESIS

Although the aetiology of MND remains unknown, current evidence suggests that multiple interacting factors contribute to motor neuron injury in MND. The working hypothesis is that MND, like many other chronic diseases, is a complex genetic condition, and the relative contribution of individual environmental and genetic factors are likely to be relatively small [4]. The three key pathogenetic hypotheses are genetic factors, oxidative stress, and glutamatergic toxicity, which result in damage to critical target proteins such as neurofilaments and organelles such as mitochondria [47-49].

Pathological findings in MND vary depending on the clinical variant. Most patients have the ALS variant where large α-motor neurons in the brainstem and spinal cord degenerate leading to progressive weakness and muscle atrophy whilst loss of upper motor neurones result in spasticity and hyper-reflexia [50]. MND is generally regarded as a multisystem disease -- motor neurons are the earliest and most prominently affected groups of cells but small interneurons in the spinal cord and motor cortex [51], and cortical motor cells are also lost. As a result, retrograde axonal loss and gliosis in the corticospinal tracts occurs, accompanied by involvement of sensory, spinocerebellar pathways and neuropsychological changes [52,53].

Mechanisms of selective motor neuron death are unclear and most current hypotheses are based on animal models [53]. These include: SOD1-mediated toxicity, excitotoxicity, cytoskeletal derangements, mitochondrial dysfunction, apoptosis and others. SOD1 converts superoxide, a toxic by-product of mitochondrial oxidative phosphorylation, to water or hydrogen peroxide. More than 100 mutations are known [31,54,55] and all but one mutation cause dominantly inherited disease. However, how mutant SOD1 leads to motor neuron degeneration is unclear. It is well established though that SOD1-mediated toxicity in MND is not due to loss of function but instead to a gain of toxic properties [56,57] as SOD1 null mice do not develop MND [58]. The role of excitotoxicity in MND is also unclear. The hypothesis is that excessive levels of excitatory neurotransmitter glutamate may initiate a cascade that results in motor neuron death. Lending support to this is the finding that glutamate levels are elevated in a subset of MND patients [59] and that riluzole, an antiglutaminergic drug improves survival in pwMND [60]. Another hypothesis is that SOD1 may induce protein aggregates that are toxic to motor neurons [61]. However, a recent study suggested that

accumulation of aggregates were more likely a result of end-stage disease rather than a contributor to MND pathogenesis [62]. Leading on from the abnormal protein aggregation hypothesis however is the cytoskeletal derangement hypothesis. Neurofilament proteins (neuron-specific intermediate filaments) are the most abundant structural protein in mature motor neurons and aggregates of neurofilament proteins are commonly seen in MND. Mitochondrial dysfunction is postulated as another mechanism as mitochrondria in MND patients show abnormal morphology and biochemistry [63].

1.5. CLASSIFICATION

The spectrum of MND can be classified into the following clinical phenotypes:

ALS is the most common form (85%) and includes upper motor neuron (UMN) and lower motor neuron (LMN) pathology.

Progressive muscular atrophy is a progressive LMN disorder and if remains confined to LMN involvement, is consistent with prolonged survival compared with ALS. In the largest study to date (n=962) [64], 91 patients initially diagnosed with progressive muscular atrophy had a longer median survival than 871 patients with ALS (48 versus 36 months). After approximately 80 months, however, the estimated survival in progressive muscular atrophy was about the same as that of ALS. Some individuals with progressive muscular atrophy never develop UMN signs clinically. However, despite the lack of signs, these patients frequently have UMN pathology [65]. In the above study, UMN signs developed in 20 of the 91 patients (22%) initially diagnosed with progressive muscular atrophy [64]. This generally occurs within two years of symptom onset.

Primary lateral sclerosis is a progressive UMN disorder. It progresses the slowest and has the longest survival compared to the other phenotypes [66]. It is also characterized by lack of weight loss, and absence of LMN findings on examination or electromyography in the first four years after symptom onset [67]. Although some individuals never develop clinical LMN signs, most do later in their clinical course [68]. There have been case reports however, of pathological findings of isolated UMN involvement [69].

Progressive bulbar palsy is a progressive UMN and LMN disorder affecting the cranial muscles. Occasionally, only bulbar involvement is seen but more commonly, UMN and LMN signs and symptoms spread to involve other areas (bulbar-onset MND).

The flail arm syndrome is characterized by progressive severe LMN weakness and wasting mainly affecting the arms (particularly proximally). There is a 9:1 male predominance [7] and these patients have a slower rate of progression both to the spread of signs and symptoms in other body segments and to development of respiratory muscle weakness [70].

The flail leg syndrome is characterized by progressive LMN weakness and wasting in the distal leg. These patients also have a slower rate of progression to involvement of other body segments and to the development of respiratory muscle weakness [70].

It is now clear that a proportion of MND patients have additional features such as frontotemporal dementia, autonomic insufficiency, parkinsonism, supranuclear gaze paresis, and/or sensory loss. These patients may be considered to have “ALS plus syndrome” [7].

1.6. DIAGNOSIS

The diagnosis of MND is clinical and includes the presence of UMN and LMN signs, progression of disease and the absence of an alternative explanation. There is no single diagnostic test at present that can confirm or entirely exclude the diagnosis of MND. Clinicians rely mainly on clinical history and examination, supported by electrodiagnostic studies and negative findings in neuroimaging and laboratory studies. Clinically, asymmetric limb weakness is the most common presentation (80%). In upper limb onset, patients may report difficulty with fine-motor tasks such as buttoning or writing. In lower limb onset, patients may report issues resulting from foot drop, such as tripping whilst walking or running. Bulbar onset is next most common (25%) with reports of slurred speech or swallowing difficulties. Occasionally, pain and muscle cramping, fatigue, weight loss, dyspnoea or other respiratory symptoms may be the initial symptoms [71]. Physical findings may confirm UMN involvement (weakness, spasticity, hyperreflexia, slowness of movement, extensor plantar responses) and LMN involvement (fasciculations, muscle wasting, weakness). Electrodiagnostic studies involve electromyography (EMG) and nerve conduction studies. EMG aids identification of LMN loss – the most frequently recognised abnormalities on EMG are fasciculation and spontaneous "denervation" discharges (fibrillation potentials and positive sharp waves) [72]. Nerve conduction studies are important to exclude differential diagnoses. Motor conduction block should be absent in MND and motor and sensory conduction velocity and compound motor action potentials should be (almost) normal in both arm and leg [73]. Differential diagnoses are shown in Box 1.1.

Box 1.1. Differential diagnoses of MND [71]

Disorders that focally involve the spinal cord
- cervical and lumbar spondylosis
- multiple sclerosis, syringomyelia
- tumours
- aterio-venous malformations
- infarction
- congenital dysplasias of the brainstem of spinal cord

Neurogenic and myogenic diseases with LMN symptoms similar to MND
- multifocal motor neuropathy with conduction block
- postpoliomyelities
- muscular atrophy
- Kennedy's disease
- paraneoplastic neuropathy
- inclusion body myositis

Others
- myasthenia gravis
- heavy metal intoxication
- hyperthyroidism
- hyperparathyroidism
- Joseph disease
- hexosaminidase A deficiency

The list of differential diagnoses is rather extensive, yet most other diagnoses can be ruled out through careful history, physical examination, and selective diagnostic testing, which may include MRI of the brain and spine, electrodiagnostic studies, complete blood count, serum chemistries, and thyroid function tests. Heavy metal screen is indicated only if there has been exposure. Antiganglioside antibodies (GM1 antibodies) may be helpful in the setting of multifocal conduction block [71]. The (Revised) El Escorial World Federation of Neurology criteria [74,75] were designed for research purposes but allow an assignment of diagnostic certainty (see box 1.2 and 1.3).

Box 1.2. El Escorial criteria for the diagnosis of MND/ALS [74]

The diagnosis of MND/ALS requires:

A. the presence of:

(A:1) evidence of LMN degeneration by clinical, electrophysiological or neuropathologic examination,

(A:2) evidence of UMN degeneration by clinical examination, and

(A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together with

B. the absence of:

(B:1) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and

(B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Box 1.3. Diagnostic categories based on El Escorial criteria for the diagnosis of MND/ALS [74,75]

Clinically Definite ALS: is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in three regions.

Clinically Probable ALS: is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

The terms Clinically Probable ALS - Laboratory-supported and Clinically Possible ALS are used to describe these categories of clinical certainty on clinical and laboratory criteria or only clinical criteria:

Clinically Probable - Laboratory-supported ALS: is defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Clinically Possible ALS: is defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable - Laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically possible ALS.

Clinically Suspected ALS: it is a pure LMN syndrome, wherein the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study. Hence, this category is deleted from the revised El Escorial Criteria for the Diagnosis of ALS.

In clinical practice however, the El Escorial criteria are too stringent; as a result early MND is missed and 25% of patients may die from MND without ever meeting the criteria [76,77]. In 2006, a consensus meeting held at Awaji-shima aimed to resolve these issues by recognising the equivalence of clinical and EMG data in detecting chronic neurological change, thus integrating EMG and clinical neurophysiological data into an algorithm [78]. The application of the 'Awaji algorithm' to the revised El Escorial diagnostic criteria for diagnosis of MND appears to increase the sensitivity of the El Escorial criteria for MND diagnosis (95% sensitivity vs 18% using clinical El Escorial criteria and 53% combining clinical and EMG El Escorial criteria)[79] without losing specificity [80]. This increased sensitivity applies in particular to bulbar onset patients (sensitivity improved from 38% to 87%) and for patients with El Escorial "clinically possible ALS" (from 50% to 86%) [78].

1.7. MEASUREMENT TOOLS

There are a number of outcome measurement tools used in MND. They can be broadly divided using the ICF framework [8] into those that measure impairment and activity limitation ("disability") and those that measure participation limitation ("handicap") and quality of life. There is often overlap, however, in the domains as most outcome measures precede the introduction of the ICF framework. Some measures are MND-specific whilst others are generic.

A range of impairment and activity limitation measurement tools are listed in box 1.4. The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) is currently the most commonly used. It was developed to enable measurement of a broader range of "disabilities" and minimise inclusion of impairment measurements to allow analysis of disability components [81], and was revised in 1999 to incorporate assessments of respiratory function [82]. The revised version is a 48-point measure with excellent validity and reliability, and can be administered over the phone [83]. It is determined by scoring 0-4 for each of the twelve domains (speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnoea, orthopnea and respiratory insufficiency). A lower score indicates more disability.

Box 1.4. Impairment and activity limitation measurement tools used in MND

Generic measures [84] Functional Independence Measure [85] Barthel Index [86] Rehabilitation Activities Profile [87] Frenchay Activities Index [88]
MND-specific measures Norris Amyotrophic Lateral Sclerosis Scale [89] Appel Amyotrophic Lateral Sclerosis Scale [90] ALS Severity Scale [91] Amyotrophic Lateral Sclerosis Functional Rating Scale [92]

Participation limitation is a significant issue from the perspective of pwMND and their caregivers [11], yet it is poorly covered by existing outcome measurement tools. Given the relentlessly progressive and fatal nature of MND, quality of life is one of the most important areas to address in MND. However, quality of life is a broad concept, and not easily incorporated in a single outcome measurement. Most outcome measures are generic and may not be sensitive to changes specific to a rapidly progressive condition such as MND. Within the generic measurement tools, some measure health-related status (for example, SF-36 or Sickness Impact Profile) whilst others are more specific for measurement of quality of life [eg. McGill Quality of Life Questionnaire, direct-weight version of the Schedule of the Evaluation of Individual Quality of Life (SEIQoLDW)] [93]. The SEIQoLDW [94] is useful as it can be used for both patients and their caregivers. However, this scale is time intensive [95] and whilst it may be of great value in identifying those factors which contribute to the psychosocial well-being of an individual with MND, it does not necessarily reflect aggregate quality of life in pwMND [96]. Although measures specific for MND, such as the ALSAQ-40 [97] have been developed for use, they have yet to be widely taken up. Some are heavily weighted towards physical function (e.g. ALSAQ-40) and do not include an existential element (perception of purpose, meaning of life, capacity for personal growth) relevant for pwMND [93]. Recently, a modified version of the McGill questionnaire was validated as an MND-specific quality of life questionnaire (the ALSSQOL) [98], and a shortened version is currently undergoing validation in a multi-centre study.

Choice of outcome measures is a significant issue in MND clinical trials. The outcome measures used may not capture the entire spectrum of issues in MND, nor reflect change adequately. Whilst survival is clinically important and easy to measure, there are several reasons to consider use of other outcomes [99]. Survival can be influenced by many interventions that do not clearly alter disease progression, such as enteral feeding [100]. The use of survival as an endpoint also mandates large trials that treat patients for long periods of time, thus very few patients will experience the event being measured [99]. Most importantly, the objective of many trials is not to alter the underlying pathology of disease but to reduce symptoms and limitations at the level of activity and participation, and to improve quality of life, hence outcome measures should address these domains.

1.8. Pharmacological Management

Riluzole is the only drug that has been shown to prolong survival (by about two to three months) [60]. Although the precise mechanism of action in MND is unclear [101], riluzole is thought to reduce glutamate-induced excitotoxicity by inhibiting glutamic acid release, blocking NMDA-receptor mediated responses and by direct action on the voltage-dependent sodium channel [102].

A dose of 100mg daily is reasonably safe. The elimination half-life is 12 hours and the recommended dosing is 50mg twice daily. Riluzole is generally well tolerated and the most significant adverse effects are gastrointestinal and hepatic. These are mostly reversible after stopping the drug.

Costs of riluzole are relatively high (approximately $10,000/year in the US)[60] and it is approved only in select countries (eg. USA, Australia, Canada and many European countries).

Current guidelines [103,104] recommend treatment as soon as possible after diagnosis with the following criteria predicting those most likely to benefit: "definite or probable ALS" by El Escorial criteria, symptoms present for less than five years, vital capacity of greater than 60% of predicted and no tracheostomy.

Unproven treatments are an area of increasing interest to physicians and patients alike. It has been estimated that almost 80% of patients take high-dose vitamins, minerals, or other nutriceuticals despite no proof of benefits for any of these in MND (only creatine and vitamin E have been examined for efficacy) [105]. Whilst many drugs have shown promise in preclinical trials, to date none have proven to be of benefit in MND (apart from riluzole) in human clinical trials (see Table 1.1) [106]. A frequently updated list can be found on the ALS Association website (www.alsa.org).

Table 1.1. Drug treatments with unproven outcomes in MND (adapted from [104])

No benefit observed:
– N-Acetylcysteine
– Ciliary neurotrophic factor (CNTF)
– Verapamil
– Gabapentin
– Topiramate
– Lamotrigine
– Celecoxib
– Minocycline [107]
– Coenzyme Q10 [108]
– Insulin-like growth factor (IGF-1)
– Selegiline
– Vitamin E
– Creatine monohydrate
In trial phase:
– Arimoclomol
– Ceftriaxone
– Gene therapy
– Lithium*
– Pramipexole
– Talampanel
– Memantine

*A recent double-blind randomized controlled trial in the United States and Canada was stopped early for futility and it is likely that lithium will not demonstrate therapeutic benefit [109].

Although some of these drugs are currently available for other indications, off-label use in MND is not recommended for a number of reasons [110] including:

- Lack of intensive safety measures outside of a clinical trial. For example, information showing poor outcomes for treated patients in the minocycline and topiramate trials became apparent only after grouped data were studied.

- Using an off-label medication during the conduct of a clinical trial can impede or slow enrolment in a trial, which has the effect of increasing risk to subjects in the trial.

There is also a range of treatments other than drugs with variable safety profiles from "benign" nutritional supplements to potentially dangerous therapies such as chelation, dental amalgam removal, or administration of unknown substances said to be stem cells [110].

MND is a life-threatening disease, but clearly some treatments can reduce quality or length of life; hence it is critical for patients to be given the information they need to avoid these [110].

1.9. MULTIDISCIPLINARY CARE

1.9.1. Definition of Multidisciplinary Care in MND

With no cure currently available, the challenge in MND is to prolong independence, prevent complications and optimise quality of life. This is best met by a multidisciplinary team with a focus on symptomatic, rehabilitative and palliative care [103,104]. The multidisciplinary team (see figure 1.1) comprises of a group of clinical professionals with expertise in MND, directed by a physician, who work as an integrated unit to provide seamless care which is patient-centered, flexible and responsive to the evolving nature of the condition [111], and aims to maximise activity and participation. The literature presented in this review includes all levels of evidence for multidisciplinary care of MND (including randomised and clinical controlled trials, case studies and expert opinion).

1.9.2. Evidence for Multidisciplinary Care in MND

A recent Cochrane review [112] found that in the absence of randomised controlled trials, the 'best' evidence to date (based on five observational studies) suggests some advantage for quality of life without increasing healthcare costs, reduced hospitalisation and improved disability. The evidence for survival is conflicting. However, the absence of proof that multidisciplinary care is effective must not be interpreted as proof that this approach is ineffective. There are multiple, well-defined interventions, such as nutritional support and respiratory support, and interventions by physical, occupational and speech therapists which have individually had significant impact on disease course. Hence, the gap in available trial data showing efficacy when offered simultaneously in a multidisciplinary setting should not at all implicate therapeutic nihilism in the treatment of MND.

1.9.3. Applying the ICF Framework to Multidisciplinary Care in MND

Rehabilitation is defined as 'a problem solving educational process aimed at reducing disability and increasing participation experienced by someone as a result of disease or

injury' [113]. Although it is sometimes effective in reducing impairment, its principal focus is to reduce symptoms and limitations at the level of activity and participation, through holistic interventions, which incorporate personal and environmental factors. The rehabilitation perspective is much broader than the 'medical' perspective, and emphasizes the understanding that a person's health and functioning is associated with a condition or disease, and not merely a consequence of it. The rehabilitation model works well with the World Health Organization's ICF framework [114], which is multifaceted. It includes the perspectives of the physicians with regards to the management of complex and interacting symptoms in MND, the therapists' views in terms of managing change in functional status in activities of everyday living and importantly, also the perspective of the pwMND and their caregivers, which may differ from the others.

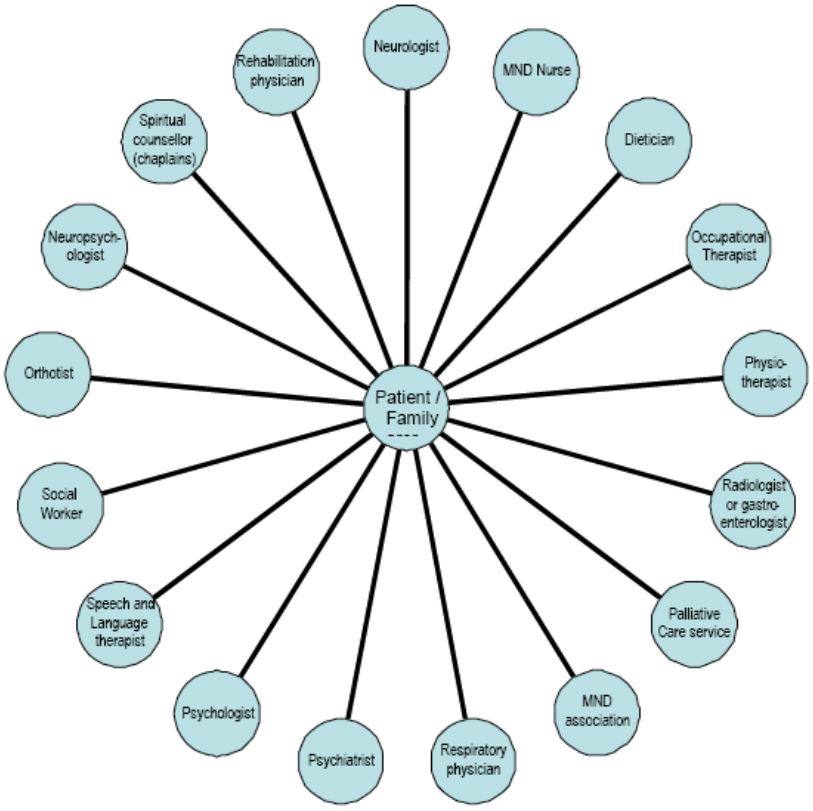

Figure 1.1. The multidisciplinary team in MND (adapted from [111]).

The aim of the ICF classification system is to provide a common language and framework for the description of health and health-related states. The domains in the ICF are divided into a) Body Functions and Structures; and b) Activities and Participation. These terms replace the previously used terms 'impairments' and 'handicap'. The ICF domains for people with a health condition such as MND describe what a pwMND can do or does do. 'Functioning' is an umbrella term encompassing all body functions, activities and participation; similarly 'Disability' includes impairments, activity limitations or restriction in participation. The ICF acknowledges that environmental factors (physical, social and

attitudinal environment in which people live and conduct their lives) and personal factors (intrinsic influences such as self-efficacy, positive adaptation) interact with all the other constructs within the ICF (see figure 1.2).

A pwMND can therefore present to rehabilitation with various combinations of deficits, which can be classified according to the ICF:

- "Impairments" are problems with body (anatomical) structures or (physiological) function (such as weakness, spasticity, dysphagia).
- "Activity limitation" (disability) describes the difficulties that a person may have in executing everyday tasks (reduced mobility and self care, pain).
- "Restriction in participation" relates to problems experienced by a person with involvement in societal participation and life situations (driving, work, family,
- psychosocial activities).
- "Contextual factors" include:
  - 'environmental' factors (such as access to medical care); and
  - 'personal factors' including gender, race, self-efficacy, coping style and social and educational background.

All these constructs combine to affect the person's experience of living with their condition.

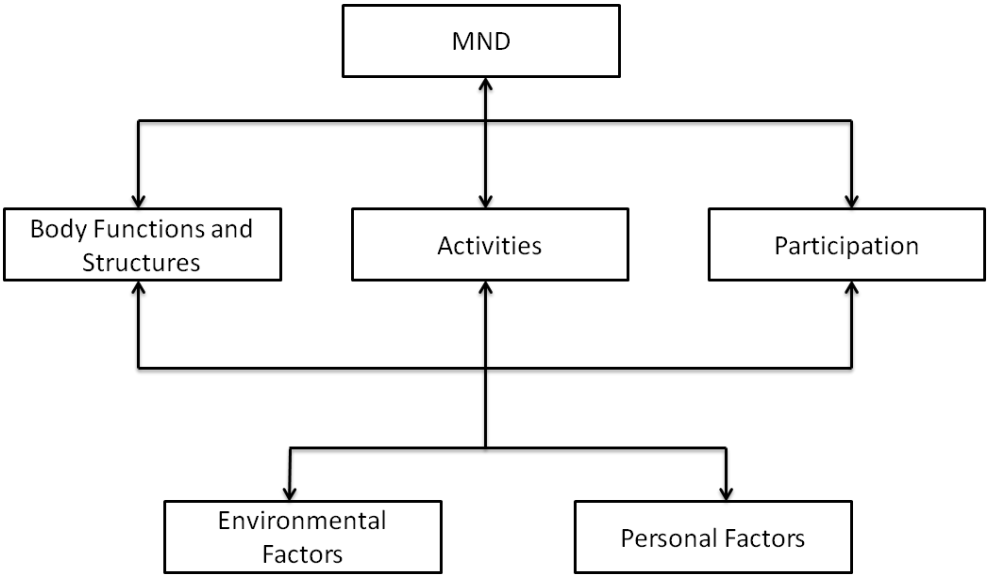

Figure 1.2. The interactions between the various components of the ICF (adapted from [114]).

The ICF can be used to further facilitate and optimise clinical care through the development of "core sets". These are ICF categories selected by experts (patients, caregivers, clinicians) that list issues in impairment, disability, participation environmental factors that need to be addressed in multidisciplinary care settings. This has been done in other neurological conditions such as stroke [115], multiple sclerosis [116] and Guillain-Barré syndrome [117]. A set of relevant ICF categories has not been identified in MND and would

be very useful in both clinical and research settings given the rare incidence of MND and diverse and challenging nature of the symptoms. It has also been highlighted that current outcome measures do not capture the entire spectrum of issues in MND (see section 1.7 Measurement Tools); use of the ICF could contribute towards development of appropriate outcome measures for MND.

1.9.4. Service Models and Standards: Interface between Neurology, Rehabilitation and Palliative Care

MND is a 'progressive' long-term neurological condition. The symptoms in MND are diverse and challenging and include: weakness, spasticity, imitations in mobility and activities of daily living, communication deficits and dysphagia, respiratory compromise, fatigue and sleep disorders, pain and psychosocial distress [1]. The National Service Framework [118] was developed by the department of Health in the UK to provide quality requirements for the inspection authorities (the Healthcare Commission and the Commission for Social Care Inspection) to use in measuring local progress for long-term neurological conditions. It advocates the need for integrated care and joined-in services in the delivery of multidisciplinary care. Included within its guidelines are 11 Quality Requirements, which make recommendations for specialist neurology, rehabilitation, and palliative care services to support pwMND to the end of their lives. The interface between neurology, rehabilitation and palliative care ensures co-ordinated care for pwMND rather than duplicating services.

Current guidelines [103] state that specialized multidisciplinary clinical referral should be considered for pwMND to enable optimal health care delivery. However, even within multidisciplinary clinics, there is a shortfall in service provision from the perspective of pwMND and their caregivers. A recent study (n=44 pwMND, n=37 caregivers of pwMND) [11] showed that despite a universal health system (Medicare) and accessibility to a specialised MND multidisciplinary clinic, gaps included a) the limited understanding and availability of assistive technology to facilitate function and decrease reliance on caregivers, b) advice regarding employment and driving and c) limited psychosocial support from the caregivers' perspective. In a different study also based in Australia (patient n=503, caregiver n=373) comparing the extent to which existing supportive service models met the needs of four neurodegenerative disorders (MND, multiple sclerosis, Parkinsons' disease, Huntington's disease), the caregivers of pwMND reported the lowest quality of life and were most distressed by fatigue and tiredness [119].

The gaps in service most likely relate to a) variations in service by local community providers compounded by the absence of care by rehabilitation or palliative care physicians, b) lack of consensus about what issues should be addressed in multidisciplinary care programs for pwMND that incorporates the patients', caregivers', and treating clinicians' perspective and c) poor understanding of allied health roles. The healthcare needs of pwMND can be difficult to determine due to variable MND disease severity and progression. The limitations in activity and participation can be subjective and are not always easy to quantify with the differing perspectives of the pwMND, their caregiver, treating health professionals and by the community as a whole. The 'insider' lived experience of disablement is important in the context of providing effective clinical care. Information from such insights can guide

service policy, planning, development and resource utilization. Use of the ICF for this purpose has been discussed in Section 1.9.3.

The recent guidelines for persons with long-term neurological conditions (including MND) recommend the interface between neurology, rehabilitation and palliative care to address the diagnostic, restorative and palliative phases of illness [120]. Neurologists assess, diagnose and manage disease. Involvement of palliative care physicians at an earlier stage of disease is important for management of distressing symptoms (such as nausea, vomiting and breathlessness). While rehabilitation physicians can contribute to care by assisting with disability management and adaptive equipment provision (such as strategies and aids for communication, mobility and ability to perform activities of daily living; procedures for spasticity, pain control; and behaviour management), they can struggle as disease advances, while palliative care teams may struggle at stages where disease is not advancing. These issues may be addressed by cross-referral and closer collaboration between different services.

A proposed model for service interaction in caring for persons with MND shows involvement of neurologists and palliative care teams in the acute and terminal phases of care, with a relatively smaller role for rehabilitation physicians. However rehabilitation plays a major role in long-term care and support (over years) in the more slowly progressive phase [120].

Early rehabilitation intervention and treatment has much to contribute to improve health and quality of life prior to accumulation of disability through symptomatic and supportive therapies to enhance functional independence and community integration and reduce barriers (such as lack of knowledge about treatment, economic constraints) [121]. Disability management in MND should also be planned, with deficits should be anticipated (over time) to avoid 'crisis management'. Early palliative care intervention too has much to offer particularly in symptom management, respite care, and in addressing the psychological and spiritual issues that have been shown to have a greater bearing on quality of life in MND than physical functioning. An earlier palliative care referral allows the development of a relationship of trust while communication is generally easier, and mutual education and support of treating physicians and other disciplines in issues around communication and dying [122].

As patients deteriorate the rehabilitation and palliative care approaches can overlap, i.e. 'neuropalliative rehabilitation'. Key skills in neuropalliative rehabilitation include: understanding disease progression, symptom control, managing expectations, issues relating to communication, addressing end of life issues, legal issues (mental capacity, wills), specialist interventions (ventilation), equipment needs, counselling and support, and welfare advice [120].

The gaps and deficiencies in MND care and services need to be addressed by collaborative work practice - clinicians need to respect others with expertise in related areas; co-ordination should occur between services; communication between specialties and between specialist and local services needs to improve [123,124].

1.10. MULTIDISCIPLINARY CARE ISSUES IN MND

MND is a fatal disease with a challenging progressive course that results in a broad and ever-changing spectrum of care needs. Symptoms are varied (see box 1.5) and need to be carefully assessed and managed. The timing of provision of appropriate care is important as whilst information needs to be provided when patients are psychologically in the right frame of mind, the options of certain interventions may be time-limited as the disease continues to progress.

Box 1.5. Symptoms experienced by MND patients (adapted from [125])

Weakness 94%
Dysphagia 90%
Dyspnoea 85%
Pain 73%
Weight loss 71%
Speech issues 71%
Constipation 54%
Cough 48%
Sleep issues 29%
Emotional lability 27%
Drooling 25%

1.10.1. Respiratory Management

Most deaths in MND are due to respiratory failure as a consequence of respiratory muscle weakness, hence the diagnosis and management of respiratory symptoms is important (figure 1.3) [105]. Counselling may be initiated at the time of diagnosis especially if respiratory symptoms are present and/or forced vital capacity (FVC) is <60% of predicted. Early symptoms may be suggestive of nocturnal hypoventilation (eg. frequent arousals, morning headaches, excessive daytime sleepiness, vivid dreams) rather than overt dyspnoea [105]. It is important to discuss the options of respiratory choices, including tracheostomy and ventilatory support well before these are clinically indicated to enable advance planning or directives. It is also important to offer patients information about the terminal stages of MND and reassure regarding terminal hypercapnoeic coma and resulting peaceful death, as many may fear "choking to death" [126].

Respiratory function should be evaluated every three months from the time of diagnosis. Whilst FVC is the most commonly used [127] and significantly predicts survival [128], it can be insensitive to slight changes in muscle strength [129]. The maximal inspiratory pressure (MIP) also requires a mouthpiece. The maximal sniff nasal inspiratory force or sniff nasal pressure (SNP) may be more appropriate especially in those with bulbar weakness (no mouthpiece) and has been found to be more sensitive to changes in diaphragmatic and respiratory muscle strength [130,131]. It is also more reliably recorded in the later stages of MND and is more sensitive, although less specific than FVC for predicting six-month mortality [132].

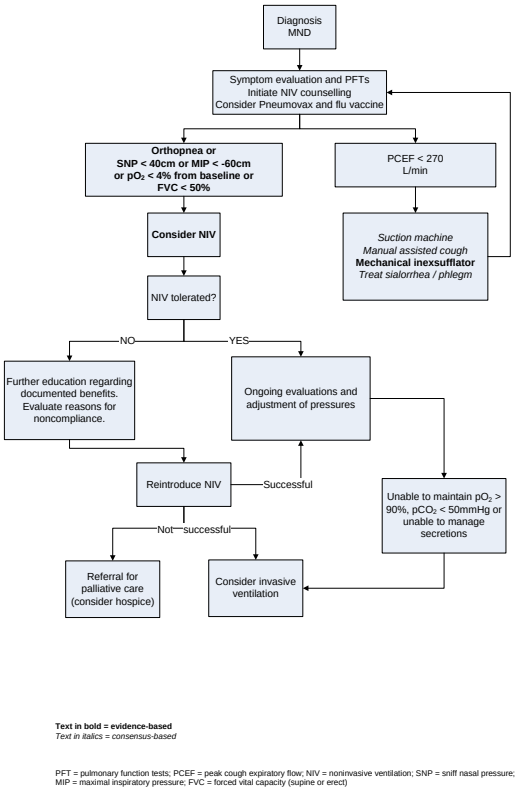

Figure 1.3. Respiratory management algorithm in MND (adapted from [105]).

Initial management can include chest physiotherapy and postural drainage, especially if the patient has difficulty clearing secretions from the chest [133]. A suction machine may also be helpful for this purpose. Preventing respiratory infections is a primary goal and pneumococcal and influenza vaccines should be administered. Respiratory muscle exercise can be instituted and may delay the onset of ventilatory failure [134].

Non-invasive ventilation (NIV) should be considered for patients with respiratory insufficiency (see figure 1.3 for criteria) and is especially helpful overnight for symptomatic nocturnal respiratory compromise although it is also often used in addition, during the day as the disease progresses. A recent Cochrane review concluded that NIV significantly improves quality of life when tolerated and may prolong survival in those with normal to moderately impaired bulbar function especially if used for ≥ 4 hours a day [135]. Successful use of NIV is dependent on respiratory therapists and patients working closely and patiently through the adjustment phase of NIV, especially with selection and tolerance of face masks. A small dose of anxiolytic may assist with the process in select patients. Bulbar involvement and executive dysfunction may also impact negatively on compliance [105].

Invasive ventilation should be offered when longer-term survival is the goal. Careful counselling is necessary with regards to benefits and burden (expense, intensive physical support with suctioning and nursing care, high caregiver burden) as many may not be able to manage invasive ventilation at home, thus requiring residential care (nursing home) placement [105,136]. Not all residential facilities manage invasive ventilation, which might further restrict options of placement. Approximately 10-20% of pwMND elect invasive

ventilation. However, of those who do undergo invasive ventilation (including those administered at the time of acute respiratory failure without advance discussion), there appears to be good acceptance and satisfactory quality of life [137].

1.10.2. Communication

Dysarthria is common as a result of bulbar involvement and can be a source of significant frustration to the pwMND and their families. Early changes include nasality or reduced vocal volume and changes in oral movement rates and speech rates [138]. As weakness and spasticity of the oral and laryngeal muscles increase, imprecise consonant production, hypernasality, harsh vocal quality, slowed rate of speech and breath volumes affect intelligibility [139]. Speech pathologists can teach the patient to slow speech rate, exaggerate articulation and improve respiratory efficiency through phrasing [1]. Palatal lift and palatal augmentation prostheses may also be of some use to reduce the hypernasal aspect of dysarthria [140]. As intelligibility worsens, augmentation of communication may be achieved with devices ranging from simple pen and paper or alphabet/word communication boards to more high-tech keyboard-based and computerised instruments. Environmental control units that use movement input from any part of the body (eg. eye gaze) can be used in very advanced disease [141]. Whilst some of these devices can be expensive, they help the patient and caregivers stay connected, respond to their need and discuss complex important issues, including medical information [142]. For those who have no voluntary motor control for communication, brain-computer interface that use electroencephalogram signals are being researched [143].

1.10.2. Swallowing and Nutrition

Dysphagia affects a third of pwMND at onset and the majority by late disease [144]. It increases the risk of suboptimal caloric and fluid intake and can worsen weakness and fatigue [145]. Aspiration pneumonia (13%) is a contributor to respiratory complications and is associated with increased mortality with mean survival time post-infection of 2 months [146].

More than 50% of pwMND report difficulties in the oral preparatory stage of swallowing (preparation of food for propulsion to the pharynx) [147]. Symptoms include jaw weakness, fatigue, drooling, choking on food and slow eating. In addition, loss of upper limb function and fear of choking or depression can further impact on self-feeding abilities and oral intake [148]. A speech pathologist can perform a bed-side assessment and/or further imaging (eg videofluroscopy) to evaluate the degree of dysphagia. Mild dysphagia can be managed with specific interventions such a alteration of food consistency, upright positioning, small bolus size, soft collar for neck extensor weakness and the chin-tuck technique, in which the person flexes their neck to the anterior chest wall as they swallow, narrowing the inlet to the larynx and reducing the chance of food aspiration. Dieticians monitor nutritional status through body weight, percentage weight loss and body mass index. Common advice includes high calorie diets, texture modification and prescription of nutritional supplements [149]. Patients may show nutritional compromise even before bulbar symptoms become significant [148] as in addition to muscle wasting, pwMND at all stages of disease often do not meet their energy

requirements [150]. Dehydration is also a common and important problem contributing to fatigue and thickened secretions [1].

As dysphagia progresses, evidence (Level B) suggests a percutaneous endoscopic gastrostomy (PEG) or equivalent (eg. radiologically inserted gastrostomy) is indicated to supplement oral intake (as long as this remains safe) for weight maintenance [151]. PEGs prolong survival but there is currently little evidence regarding the impact of PEG on quality of life [100]. Timing of a PEG can be challenging. Weight loss (a loss of 5-10% of body weight implies nutritional risk [1]) and FVC should be considered (PEGs should be placed before FVC falls below 50% of predicted [152] as risks of largyngeal spasm, localized infection, gastric haemorrhage, technical difficulties of PEG placement and respiratory arrest increase [153,154]).

Sialorrhoea can be a significant issue in MND and is generally not related to increased saliva production but rather to impaired ability to swallow saliva, combined with facial weakness causing labial incompetence and neck weakness causing the head to tip forward [1]. Improved positioning, use of a cervical collar and orolingual exercises may be helpful. Medications such as anticholinergics and tricyclics can also be trialled [155], as can suction machines. In the US, most commonly used medications are amitriptyline, glycopyrrolate, atropine and propantheline [156]. However, medications may further thicken secretions, hence should be used with caution in those with respiratory insufficiency or poor cough. More recently, botulinum toxin injected into the salivary glands (parotid, submandibular) appears to be safe and has been used to treat sialorrhea with beneficial effects lasting approximately 3 months [157,158]. Thick oropharyngeal secretions may be treated with increased fluid intake, humidification of air, cough augmentation, suction machines and guaifenesin [156].

1.10.3. Exercise

The effects of exercise and safe therapeutic range in MND are poorly understood. It is generally accepted that weakness and muscle fibre degeneration may be accelerated by overwork or heavy exercise as it is already functioning close to its maximal limits [159]. However, inactivity leads to deconditioning and disuse weakness. In addition, muscle and joint spasticity can cause pain, contractures and further loss of function. A recent Cochrane review [160] identified two trials (n = 52), which addressed therapeutic exercise in MND. The trials examined the effects of moderate intensity, endurance type exercise on spasticity, and effects of moderate intensity resistance type exercises in MND. Although one of the trials reported improvement in function and quality of life, both trials were too small to determine to what extent strengthening exercises were beneficial or harmful in this population [160]. In view of the paucity of evidence to guide exercise prescription, the current recommendations are [161]:

- Stretching exercise to improve flexibility to maintain muscle length and joint mobility and prevent contractures.
- Strengthening exercise of sub-maximal (low, non-fatiguing) intensity, with degree of resistance tailored to muscle strength.

- Aerobic/endurance exercise may improve cardio-respiratory fitness and is probably safe but adequate oxygenation, aeration and carbohydrate load is important to reduce oxidative stress load.

1.10.4. Mobility and Activities of Daily Living

In early stages of disease, rehabilitation aims to prolong independence in mobility and activities of daily living, prevent complications such as falls, contractures, and musculoskeletal pain, maintain strength, range of movement and conditioning through an appropriate exercise program, educate the patient and family about the disease, provide psychological support, evaluate the home for safety and teach energy conservation techniques [162].

As weakness worsens, the physiotherapist can instruct the patient and family in safe transfer techniques (eg. between bed and chair, in and out of cars), optimise gait pattern and provide gait re-training with appropriate gait aids (eg. walking frame, sticks) and orthoses (ankle-foot orthosis to facilitate foot clearance during gait and stabilise knee to prevent falls). Occupational therapists can fabricate with upper limb orthoses to assist with fine motor function. For example, patients with distal weakness can improve hand function with wrists braced in 30° extension which improves efficiency of grip and addition of a universal cuff can assist those with weak grasp in feeding and typing [1]. Other adaptive equipment is also provided, such as built-up cutlery for eating, Velcro fasteners for dressing, long-handled aids, and bathroom equipment (rails, over-the-toilet frames, bath boards, shower chairs, commodes).

Wheelchairs are generally eventually required although introduction of a wheelchair whilst a patient is still ambulant, for intermittent community use, is important to enhance energy conservation. Future needs should be anticipated and considered when prescribing a powered wheelchair (eg. reclining, tilt-in-space, custom seating, and modifiable control system) to optimise independence and social interaction whilst preventing contractures, compression nerve palsies, skin breakdown and aspiration. A motorised scooter may be more appropriate for some patients [1]. Other equipment such as hospital beds with pressure-relieving mattress and hoists for lifting might also be required. Caregiver training in the use of hoists is important to prevent injury.

1.10.5. Bladder, Bowel and Sexuality

Although bowel and bladder sphincters are generally spared, bowel, bladder and sexual dysfunction may be much more common (30%) than reported to health professionals by pwMND [11,163]. These areas are in general poorly studied in MND. Constipation is likely to be common with inactivity and poor nutritional intake and can be treated with a regular bowel program with intake of fibre/bulking agents and adequate fluids. Suppositories, stool softeners and enemas may be required. In a group of 38 pwMND who underwent urological evaluations, 47% had micturition symptoms and urodynamics studies found a range of UMN abnormalities [164]. Where urinary urgency is an issue, oxybutinin may be helpful.

Contributory factors to incontinence, such as urinary tract infections, drinking large amount of fluids late in the day and dependent oedema causing nocturia when the legs are elevated overnight should be considered and treated. Wasner et al [165] suggested a prevalence of 62% (n=62) in sexual dysfunction with issues including decreased libido and passivity of the patient and partner due to physical weakness and the body image changes. The wide variation in reported prevalence in bowel, bladder and sexual dysfunction suggests that patients may not volunteer this information; hence its inclusion in routine enquiries might help to encourage reporting and thus the facilitation of appropriate treatment, such as sexual counselling and suggestion of specific techniques.

1.10.6. Pain

Pain is common in MND, especially in the later stages. Musculoskeletal pain from weakness and resulting postural changes can be ameliorated with range of motion exercises, adequate support in sitting and supine positions and proper lifting and transfer techniques to prevent undue traction on weakened joints. Fatigue and depressive symptoms may also worsen a patient's experience of pain.

Spasticity and muscle spasms are not an uncommon source of pain and with the current paucity of supporting evidence, this is often treated with stretching exercises in combination with a muscle relaxant (baclofen is the drug of choice) [166]. Baclofen should be started at low doses (5mg twice to three times daily) and slowly increased (up to 100mg a day in divided doses). Baclofen however can be associated with muscle weakness. Tizanidine (2mg twice daily up to 24 mg a day) is likely as efficacious but it is associated with dry mouth. Other options include clonidine (25 µg twice a day) which can cause hypotension, drowsiness and bradycardia and benzodiazepines which can cause sedation and habituation and respiratory depression. Dantrolene is not recommended as it can cause excessive muscle weakness in MND [167]. Intrathecal baclofen is rarely required but may be indicated in those with intractable spasticity, needing more than the maximum oral dose [168]. There are few reports of use of botulinum toxin for spasticity in MND in literature. Caution is advised as pwMND may be more prone to developing generalised weakness after being injected with botulinum toxin A to treat spasticity [169].

Muscle cramps can cause severe pain and discomfort and are a result of spontaneous activity of motor units induced by contraction of shortened muscles [170]. The list of potentially useful drugs for cramps is extensive, implying efficacy of individual agents is low and variable and the evidence base weak. In the US, quinine (35%), baclofen (19%), phenytoin (10%), and gabapentin (7%) were the preferred agents [156]; in Europe, choices were quinine (58%), benzodiazepines (40%), magnesium (25%) and carbamazepine (23%) [171]. In 2006 however, the US Food and Drug admininstration restricted the use of quinine sulfate in the US to treatment of malaria faciparum because of concerns regarding severe adverse events, including cardiaarthymias, thrombocytopaenia, severe hypersentivity reactions and serious drug interaction [172].

In advanced disease, pain often results due to immobility. Adequate mattress support, range of motion exercise and frequent turning of the patient are essential. Equipment such as motorized beds that slowly rotate from the side to side can be useful for reducing caregiver burden [1]. Analgesia such as nonsteroidal anti-inflammatory drugs or narcotics (oral or

sublingual) may also be required (with careful respiratory status monitoring in the latter). Intramuscular delivery of medications should be avoided due to muscle wasting [141].

1.10.7. Fatigue and Sleep Disorders

Fatigue is a common disability in MND – 77-83% in recent studies [11,173] but understudied and often overlooked by clinicians [174]. It is unrelated to clinical strength as a large component of fatigue in MND has a central origin [175]. Fatigue in MND does not correlate directly with gender, educational level, disease duration, physical function, quality of life, dyspnoea, depression or sleepiness [173]. However, contributory factors may include sepsis (including aspiration), depression and/or anxiety, pain, hypoventilation, positioning, sleep disruption and effortful activity and these should be treated where possible. It may manifest as reduced energy, difficulty in maintaining sustained attention and increased motor weakness, incoordination and gait difficulties. No double-blind, placebo-controlled trials have been performed for treatment of fatigue. Physostigmine is sometimes prescribed but not necessarily effective [176]. Modafinil appears to be well-tolerated in a recent small open-label study (n=15) and may reduce symptoms of fatigue [177]. Rehabilitation strategies involve pacing activities (regular rest breaks), energy conservation and fatigue management strategies, addressing sleep disorders, consideration of exercise to improve fitness if appropriate and treating other exacerbating factors.

High incidence of sleep disturbance in MND has been reported with pain, micturition, and choking listed by patients as the most common causes for awakening [178]. Other contributors to poor sleep include abnormal nocturnal movements such as periodic leg movements or fragmentary myoclonus, which was demonstrated on polysomnography in almost all patients with fatigue [178]. Such movements may be treated with controlled release carbidopa-levodopa (Sinemet CR) [179]. Antihistamines (eg. diphenhydramine) and other sedatives (eg. Chloral hydrate 250-500mg, benzodiazepines) can also be considered once respiratory causes for sleep disturbance have been ruled out (see section 1.10.1 for the treatment of respiratory-related sleep disturbance).

1.10.8. Cognition and Behavioural Impairment

Cognitive impairment is increasingly recognised in MND -- 50% are thought to have frontal executive deficits (see box 1.6) [180]. Visuospatial function, praxis and memory storage are usually spared [181-183]. Use of memory aids such as diaries, planners and structured daily routine is encouraged. Other conditions (depression, anxiety, fatigue) and medications (anticholinergics, benzodiazepines) should be monitored as they can worsen cognitive function.

Behavioural changes unrelated to mood or cognition has also been noted although estimates of prevalence vary widely [184]. Marked apathy occurs in an estimated 55% of pwMND [185].This correlates with deficits in verbal fluency but not depression, disease duration, FVC or ALSFRS scores and may be related to fatigue, respiratory weakness, impaired sleep, anxiety or medication [184]. It may also be a psychological coping mechanism [184].

In a subset of pwMND (approximately 5%), clear fronto-temporal dementia (also known as fronto-temporal lobar degeneration) is the presenting picture with severe behavioural dysfunction (insidious onset with gradual progression, altered social conduct, impaired regulation of personal conduct, emotional blunting, loss of insight) that begins before motor weakness becomes obvious [184]. In addition, those with fronto-temporal dementia may exhibit disinhibition, restlessness, reduced empathy, lack of foresight, impulsiveness, social withdrawal, verbal stereotypes, verbal or motor perseveration and/or sexual hyperactivity [186].

Management of behavioural and cognitive deficits can be challenging and begins with the identification of these issues. An assessment by a neuropsychologist is often helpful in terms of defining the deficits and provision of cognitive and behavioural remediation strategies. Education and counselling of the patient and family is important. No trials have been conducted in efficacy of pharmacological interventions in this area; however the use of antidepressants and antipsychotics may be considered.

Box 1.6. Cognitive deficits in MND (adapted from [184])

Attention and concentration
Working memory
Cognitive flexibility (rigidity)
Response inhibition
Planning/problem/solving/abstract reasoning
Visual-perceptual skills
Memory
Word generation (fluency)

1.10.9. Pseudobulbar Affect

Pseudobulbar affect describes sudden uncontrollable outbursts of laughter or tearfulness and is a result of bilateral corticobulbar tract degeneration [187]. It is common, affecting between 50-70% of pwMND [188] especially those with the bulbar form of MND. Pseudobulbar affect can have a significant impact on anxiety and emotional frailty [188], social functioning and relationships in pwMND as these sudden, frequent, extreme, uncontrollable emotional outbursts may lead to severe embarrassment and social withdrawal [189].

Despite the prevalence of this issue, less than 15% ask for treatment [190]. Education of the pwMND and their family and friends assists with understanding and acceptance of these pathological and involuntary outbursts and is an important component of the appropriate treatment of pseudobulbar affect. Crying associated with pseudobulbar affect is easily incorrectly interpreted as depression; laughter may be embarrassing. Pharmacological treatment can include amitryiptiline (10-150mg nocte, starting with 10mg and slowly increasing the dose) which also has the positive benefit on weight loss and loss of appetite [190] or fluvoxamine (100-200mg daily). A more recent study (n=140) showed that dextromethorphan and quinidine in combination appears to be more effective in reducing the

frequency and severity of psudobulbar affect and to improve quality of life) [191]. However, side effects are also more common (nausea, dizziness, gastrointestinal complaints) [191].

1.10.10. Psychosocial Issues

MND is a devastating condition, which takes its toll on the patient and family especially as the disease progresses, and loss of independence occurs. Rates of depression and anxiety are reported to be 0-44% and 0-30% respectively in pwMND [192] and depression does not appear to increase in more advanced disease [193]. Quality of life also appears to be more dependent on psychological and existential factors than physical factors [194,195]. Amongst caregivers, 23% are depressed [196] and caregiver strain is often significant as a result of increased caregiving time, cognitive impairments in pwMND, emotional labour and socio-economic considerations [12,197,198]. Hence, referrals to support groups and counselling and education of patients and their families (often their caregivers) are essential. Frank discussions facilitate understanding of the disease and improve coping skills. Carer support (both physical and emotional) and respite care should be discussed. Referrals to the local MND associations are also recommended as these provide patients and families with ongoing support, resources and equipment needs. Psychotherapy should also be considered to assist with coping strategies [199]. Antidepressants such as amitriptyline and selective serotonin reuptake inhibitors may be used, the former being also useful for other symptoms such as drooling, pseudobulbar affect and insomnia. Anxiety is difficult to measure due to physical confounding symptoms such as shortness of breath, muscle cramps and restlessness. Anxiety can be treated with psychotherapy and training in relaxation and breathing techniques, as well as participation in support groups. It is generally thought that the rates of anxiety increase in the pre-terminal stage [192], hence anxiolytics at this time such as benzodiazepines should be offered. With good support, mental health and quality of life can remain stable despite deteriorating physical health [200].

1.10.11. End of Life Issues

It is important to establish an open environment of communication with pwMND and their families from the time of diagnosis. Specialist palliative care providers should be involved as early as possible. Discussions should take place early, well before specific decisions need to be made. The actual timing of when to introduce these discussions however can be challenging and will depend on a number of factors including coping skills, depression and anxiety, cultural issues and functional status [201]. Some triggers may include the patient or family initiation of discussion, severe psychosocial distress, pain requiring high dosages of analgesia, dysphagia, dyspnoea and functional loss in two body regions [201]. Given the progressive nature of the disease, the patient eventually has to choose between life-sustaining therapies (respiratory assistance, feeding tubes) and terminal palliative care whilst considering issues relating to quality of life, burden of therapies, their own wishes and those of their family. It is important that clinicians caring for MND patients and their families appreciate and communicate the significance of life-threatening symptoms, monitor decision-making capacity, ensure that multiple possible end of life scenarios are anticipated and

managed with all options provided (including hospice care), review advance care directives and comprehensively consider and aggressively manage symptoms [202].

Medications should be available for all patients who are deteriorating and may be approaching the terminal phase, although the terminal phase may be difficult to recognise as there is usually slow deterioration until a quicker change leads to death within a few days or less [203]. Medications should include morphine to relieve dyspnoea and pain, midazolam to relieve distress and agitation and glycopyrronium bromide or hyoscine hydrobromide to reduce chest secretions, delivered parenterally [203]. Cultural and spiritual issues should also be addressed [201,204]. Although many pwMND fear the terminal stages of MND, with good palliative care, the later stages can be a time of fulfilment and peace for both pwMND and their families [203].

Bereavement in MND occurs in both the patient and their family and continues, in families, after the death of the patient. Some families feel relieved of their caregiver burden and the burden of losses for the patient but also have feelings of guilt that they feel these emotions; hence support is vital in this area [205].

CONCLUSION

MND is a complex and challenging condition with no cure. As such, integrated and coordinated health care delivery and services are needed for comprehensive care for pwMND using the neuropalliative rehabilitation model with the aim of maximising activity and participation and optimising quality of life. Many areas in MND are poorly understood, with research often further hindered by the logistical and ethical difficulties. Further research is needed into appropriate study designs; outcome measurement; the evaluation of optimal settings, type, intensity or frequency and cost-effectiveness of multidisciplinary care; and the different phases of MND, covering the spectrum of care required for this patient population. The interface between neurological, rehabilitative and palliative components of care, and caregiver needs should be explored and developed to provide long-term support for this population.

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