Motor neuron disease

The last 12 months

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This article is the fifth in a series of articles on important topics in neurology.

Background
For patients with motor neuron disease (MND), the final 12 months of life can be a tumultuous period, with rapid and significant losses in function and independence, regular contact with the health system and carer stress.

Objective
The aim of this article is to provide an outline of the challenges encountered during the last 12 months of life and the role of the specialised multidisciplinary team in managing the challenges that may arise.

Discussion
While MND remains rare overall, it is likely that most general practitioners (GPs) will encounter at least one patient with MND during their career. An understanding of the complexity of this group of diseases, including management in the terminal phase, is important given the GP is a valuable member of the multidisciplinary team.

[He was] 'like a great clock winding down'.
– Eleanor Gehrig,
wife of Lou Gehrig, baseballer[1]

Motor neuron disease (MND), also known as amyotrophic lateral sclerosis (ALS) and the eponymous Lou Gehrig's disease, encompasses a group of life-limiting neurodegenerative disorders. It is characterised by a progressive loss of skeletal muscle power involving the limbs, speech, swallowing and respiratory wall muscles and, for many patients, non-motor involvement such as cognitive and behavioural changes. MND places a great and sustained burden on the family and carers of the patient.

Over the past several years, it has become apparent that MND is not just a disorder of skeletal muscle but a multisystem neurodegenerative syndrome with significant and disabling motor and non-motor manifestations.[2]

The last 12 months of the life of a patient with MND is marked by an inexorable deterioration in function, a struggle to manage at home, increasing carer involvement, more frequent hospitalisations and, eventually, the terminal phase. This article outlines the common presentation and challenges of the final year of this disease and the role of clinicians, including general practitioners (GPs), in its management.

Overview

'Motor neuron disease' is a collective term for a group of debilitating, and ultimately fatal, neurodegenerative disorders affecting upper and lower motor neurons. The most common form of MND, ALS, usually begins with limb weakness, although in approximately 20% of patients it has a bulbar onset (dysfunction of speech and swallowing). The mean period between diagnosis and death in MND is three years, with only 10% surviving longer than eight years. Primary lateral sclerosis is a pure upper motor neuron (UMN) variant of MND characterised by insidious onset and slow progression, often with a life expectancy measured in decades from diagnosis.[3]

Epidemiology

MND is a rare disease. Its incidence is approximately 1–2 per 100,000 person years and it is more common in men.[4] Its prevalence is thought to be between five and six people per 100,000 population.[5] Therefore, GPs may expect to care for at least one patient with MND during their career. The mean age of onset is 58 years.

Aetiology

For the vast majority of patients, MND is sporadic in onset and there is no known cause. For a small percentage (approximately 10%), MND is familial and most commonly autosomal dominant in inheritance. In the modern era, our understanding of the genetics of this familial cohort has grown significantly. Multiple genetic abnormalities have been elucidated and are responsible for two-thirds of familial and 11% of sporadic cases. These include the *C9orf72* repeat expansion and *SOD1* mutations, with geographical and phenotypic variability.[6]

Pathophysiology

MND affects upper and lower motor neurons. Multiple theories exist regarding its pathogenesis and site of onset, one of which is cortical dysfunction leading to motor neuron involvement via glutaminergic pathways.[7] Motor neurons are thought to be vulnerable to a variety of genetic and environmental triggers, with focal onset of symptoms that then spread to contiguous body parts.[8]

From diagnosis to the final 12 months

Given that the mean survivorship in MND is three years, the final 12 months in the life of a patient are invariably the culmination of an extended period of clinical deterioration and an escalation in care needs.[9] To set the scene for the final year, therefore, it is appropriate to examine the presentation, challenges and principles of management from diagnosis onwards.

Practical management

From diagnosis onwards, MND presents multiple clinical challenges. The GP, in conjunction with other clinicians, is critical to meeting those challenges. A summary of the common issues encountered during the last 12 months is provided in Table 1, and an approach to symptom management is provided in Table 2.

Limb weakness

The progressive loss of muscle power in the upper and lower limbs has a profound effect on function. As the disease progresses, it can result in loss of mobility and falls. The role of rehabilitation medicine, physiotherapy and occupational therapy is vital in flexibly adjusting to an evolving loss of function, assessing safety and providing functional and mobility aids. Other issues in patients with a predominantly UMN presentation are cramps and spasticity.

Bulbar deficits

Speech and swallowing are invariably affected in the later stages of MND and are sometimes presenting features. Regarding speech, understanding the thoughts, wishes and emotions of the patient remains vital throughout their illness.

Table 1. The last 12 months

Domain	Features
Mobility	Progressive decline in: • limb strength • transfers • balance • mobility • exercise tolerance Increased likelihood of: • falls
Equipment and services	Increased reliance upon: • equipment – transfer belts, hoists, hospital beds, walking aids, power wheelchairs, etc • community support services – informal network of family, friends, neighbours and faith groups – formal community support services
Nutrition, hydration and respiration	Increased dependence upon: • enteral feeding/hydration (eg PEG tube) • non-invasive ventilatory support (eg BiPAP)
The carer	• Carer stress: physical and mental health issues often escalate, necessitating an increase in frequency and duration of support services and planned, periodic, respite care; social worker becomes pivotal
Cognition, behaviour and mood	• FTD progression, with impaired planning, insight and judgement • Increased depression, anxiety and emotional lability
Communication	• Bulbar dysfunction with deteriorating voice intelligibility secondary to hypophonia and dysarthria, followed by anarthria • Increased reliance on augmentative communication devices
Symptom control	• Symptom management involves oral secretions, bowel care, pain control and pressure area care
Residential care	• Residential care may be required once the burden of care outstrips available domiciliary-based care resources
Terminal phase	• Deprescribing of routine medications • Prescription of terminal care medications • Enacting an advance care plan and limits of care • Pastoral care • Death is usually linked to respiratory failure +/– infection
After-care	• Bereavement phase: pastoral care, counselling and ongoing social work support

BiPAP, bilevel positive airway pressure; FTD, frontotemporal dementia; PEG, percutaneous endoscopic gastrostomy

Responses to this deficit vary from patients writing on a notepad, using e-tablet devices with apps that convert typed text into a synthesised voice, through to, when the person has lost upper limb power, eye gaze technology that uses eye movement to communicate via a computer interface.

Dysphagia presents significant issues regarding convenience, custom and safety in ingesting food and fluids. The first sign of swallowing weakness is often coughing with liquids. Two main approaches are employed. In the early stages patients are recommended food and fluids that have a safer consistency, including adding thickening powder to fluids and converting to a soft diet. A further option is to consider the insertion of a percutaneous endoscopic gastrostomy (PEG) tube. This should be discussed early, as a late referral may coincide with respiratory muscle weakness, with the patient deemed too great an anaesthetic risk. Patients may or may not consent to a PEG insertion.

Respiratory dysfunction

Respiratory muscle involvement occurs early in MND and is associated with reduced survival. The first presentation of this weakness, well before the onset of daytime symptoms, is sleep-disordered breathing in the form of nocturnal hypoventilation that results in unrefreshing sleep, morning headache, excessive daytime somnolence and fatigue.[10] Patients should be referred early in the disease course to a respiratory physician for assessment. If considered suitable, patients are offered non-invasive mechanical ventilation (NIV) therapy, firstly overnight, and later extending to daytime and sometimes continuous usage. NIV has been shown to improve quality of life and survival in MND,[11,12] but timing of initiation and monitoring measures are still unclear.[13] NIV is not always tolerated, especially in patients with bulbar dysfunction. There may be issues with leakage and skin trophic changes, which may be ameliorated by changing the type of mask used.[14] Dyspnoea is a common symptom and may be helped by both non-pharmacological strategies such as upright positioning and medications such as opiates.[15] Refer to the section 'Modes of death'.

Salivary issues

Patients with MND are often troubled by significant alteration in the volume and/or consistency of saliva.[16] Patients can present with excessive salivation (sialorrhoea), viscous saliva and, less commonly, xerostomia. Each requires specific management, as outlined in Table 2.

Pain

Pain is a common symptom, occurring at all stages and correlating with quality of life.[17] The pathophysiology of pain in MND is likely to be multifactorial in origin and includes muscle cramps, spasticity, pressure sores from NIV masks, and neuropathic and arthritic pain. Finding a specific underlying cause may not always be successful and a variety of therapies are tried, such as simple analgesics, opiates, neuropathic pain relievers (gabapentin, pregabalin and tricyclic antidepressants) and cannabinoids.[18] A Cochrane review has not demonstrated success with any of these options.[19]

Fatigue

Fatigue can be disabling in MND and has been demonstrated to originate from both muscle weakness and impaired sleep quality and duration.[20] There has been very little work on management of fatigue but a Cochrane review found possible evidence for modafinil and respiratory exercises.[21]

Cognition and behaviour

Approximately 10–15% of MND patients also develop frontotemporal dementia (FTD).[22] This manifests as executive dysfunction with disinhibition; derangements of language, memory and social cognition may also be seen.[23] Patients may have little insight or empathy for the levels of exhaustion and stress their partner and other family members are experiencing. In addition to a formal diagnosis of FTD, nearly 50% of MND patients will develop some degree of pre-frontal dysfunction. Cognitive impairment can have a deleterious effect on disease progression, quality of life (especially for carers) and survival.[23,24]

Metabolism, nutrition and dietary supplements

There is now evidence of altered energy metabolism in MND with an epidemiological link to low body mass index.[25,26] Patients have a higher incidence of impaired glucose tolerance and diabetes mellitus.[27,28] The role of hyperlipidaemia and statins is controversial at present.[29–31]

Nutritional factors associated with reduced survival in MND are weight loss, malnutrition and severe dysphagia.[32] Progressive weight loss is associated with worsening motor symptoms and reduced survival.[33] Oral intake may be affected by a number of factors in MND: dysphagia, upper limb weakness (preparation and manipulation of food), mood disorders, fatigue, increased time for task completion and salivary disorders.[34] In patients with MND with dysphagia, the early introduction of enteral nutrition to prevent weight loss and high calorie feeding both improve survival.[35,36] Enteral feeding should be considered following loss of 5% of baseline body weight, or when intake does not meet requirements.

Protein supplementation helps to limit weight loss in MND and stabilise functional decline.[37] The effect of a high carbohydrate diet was found to meet study end points of safety and tolerability in a small study, but also had a small and statistically insignificant effect on weight gain and survival compared to high fat and isocaloric diets.[36]

Approximately 80% of MND patients use nutraceuticals such as vitamin and mineral supplements.[38] There is no evidence to support the use of magnesium, cannabinoids or quinine for cramps in MND patients, and quinine has a number of significant potential side effects.[34] Hypovitaminosis D in MND may correlate with faster functional decline, hence this should be actively treated.[39,40] High dietary intake of antioxidant-rich foods, carotenoids, vegetables and fibre is associated with some functional improvement in MND patients.[41]

Medications

The management of MND focuses mainly on symptomatic and supportive

treatment. Currently, only one medication, riluzole, has been approved globally for use in MND. It slows the progression of the disease modestly, extending mean survivorship by three months.[42] In addition, it may also delay the development of respiratory weakness.[43] That benefit dissipates over time and it is appropriate to cease Riluzole in advanced MND. The GP can be involved in this discussion. Edavarone has also received US Food and Drug Administration (FDA) approval for use in early MND; however, its efficacy is uncertain.[44] There are ongoing trials concentrating on gene therapy,[45] but these are unlikely to be useful in the setting of the last 12 months.

Support for carers

Over time, devoted family members of patients with MND may become physically and emotionally exhausted. They may become defined only by their carer role (rather than as spouse, child, or other). Patients with frontal changes may have little insight or empathy, and behavioural issues may be difficult to manage. The impact of progressive changes in needs on the spousal or parental relationship can be extreme. The GP, in conjunction with the whole multidisciplinary team (MDT), is crucial in the provision of emotional and practical support to the carers.

General management principles

Throughout the course of MND, there are several important management principles.

The role of the GP

The GP is at the nexus of the patient-centric approach that is adopted to manage MND. Generally, of all the members of the MDT, the GP has the longest connection with a patient and the best understanding of the patient prior to the illness, and of their life and family dynamics. Their role includes managing comorbidities, developing GP Management Plans and team care arrangements, participating in the MDT symptom management, advance care planning and care of the dying patient. They will support the family through the illness and into their bereavement. Ideally, GPs can link to MND clinics and participate via telehealth. For a list of MND services in Australia, refer to Appendix 1 (available online only).

Table 2. Symptom management in motor neuron disease[58]

Common issues	Management
Fatigue	• Energy conservation techniques • Work simplification methods • Support services • Non-invasive ventilation • Check haemoglobin, iron studies, thyroid function, etc
Sialorrhoea	• Anticholinergic agents, including combination preparations containing hyoscyamine, atropine and hyoscine; atropine drops orally; glycopyrrolate; tricyclic antidepressants • Injections of botulinum toxin into salivary glands • Low-dose, unilateral, salivary gland radiotherapy
Viscous/tenacious sputum	• Patient to suck on partially frozen juice of dark grapes, pineapple or papaya – these contain mucolytic/proteolytic enzymes • Nebulised normal saline • Mucolytic pharmaceuticals: bromhexine; nebulised N-acetyl cysteine
Xerostomia (uncommon)	• Maintain hydration • High fluoride toothpaste twice daily • Artificially sweetened chewing gum • Artificial saliva preparations • Cessation of drying agents, where possible (anticholinergics/ diuretics) • Oral pro-cholinergic drops (eg pilocarpine hydrochloride)
Spasticity	• Orphenadrine, baclofen, dantrolene – monitor liver function closely • Gabapentin, pregabalin, clonidine • Botulinum toxin injections • Physiotherapy • Orthoses
Respiratory dysfunction	• Monitor with respiratory function tests; polysomnography • Non-invasive ventilatory support (eg BiPAP) • Low-dose benzodiazepines/morphine
Bulbar dysfunction	• Early speech pathologist involvement • Dysphagia and aspiration: modified diet consistency (eg puree, fluid thickeners), modified cups and utensils, manoeuvres to limit laryngeal penetration, enteral feeding • Hypophonia: voice amplification system (eg lapel microphone and pocket speaker) • Dysphonia, aphonia; dysarthria, anarthria: communication boards; smartphone and e-tablet apps, eye gaze technology
Pain	• Paracetamol, anti-inflammatory drugs, opioids, gabapentinoids, TCAs, intra-articular depot glucocorticosteroid injections, physiotherapy

Table continued on the next page.

The critical role of a multidisciplinary team

International guidelines on the management of MND recommend that

Table 2. Symptom management in motor neuron disease[58] (Cont'd)

Common issues	Management
Constipation	• Maintain hydration • Dietary manipulation • Cessation of drying agents, where possible (eg anticholinergics, diuretics) • Aperients, suppositories, enemata
Weight loss	• Early dietetics involvement • Treatment of reflux and nausea • Nutritional supplements • Timely insertion of PEG, or radiologically inserted gastrostomy
Mood disorders; emotional lability	• Social work, pastoral care, psychology and psychiatry input • Anxiolytics and antidepressants
Mobility and falls	• Physiotherapy, hydrotherapy, orthoses (eg ankle–foot orthoses), hip protectors, personal response alarms
Head control	• Cervical orthoses (eg soft collar)
Activities of daily living and driving	• Early occupational therapist involvement for self-care re-training, home assessments, provision of equipment and modifications, driving assessments

BiPAP, bilevel positive airway pressure; PEG, percutaneous endoscopic gastrostomy; TCAs, tricyclic antidepressants
Adapted from Lau FS, Brennan FP, Gardiner MD, Multidisciplinary management of motor neurone disease, Aust J Gen Pract 2018;47(9):593–97. doi: 10.31128/AJGP-02-18-4495.

patients are cared for by an MDT of health professionals.[46,47] There is good evidence that care delivered by a specialised MDT confers a significant survival advantage over standard outpatient care.[48,49] In addition, an MDT has been shown to improve the health-related quality of life of patients.[50] The members of the MDT are many and varied, with core elements comprising medical practitioners: the GP, neurologist, palliative care physician, rehabilitation medicine physician, respiratory physician and a gastroenterologist. Specialist nursing care is pivotal, as is the allied health team: social worker, physiotherapist, occupational therapist, speech pathologist, dietitian, and so on.

The early involvement of palliative care

An important member of an MND MDT is a palliative care health professional. Their skills in symptom management, communication, advance care planning and the care of the deteriorating and dying patient are crucial to the role of the MDT, from the time of diagnosis onwards. Specialist palliative care confers benefits for symptom control and quality of life in neurodegenerative diseases, including MND, and palliative care professionals have a role in assisting GPs with challenging symptom management. Unfortunately, barriers continue to exist in the timely referral to palliative care. Those barriers include misconceptions that palliative care only applies to dying patients, is singularly focused on malignancy and will remove hope.[51] Patients and families, keen to maintain their independence, may also be reluctant to engage with palliative care.

A systematic approach

The progression of MND invariably involves multiple, and often simultaneous, loss of functions. This may be seen by the patient and family as chaotic and deeply distressing. One of the greatest gifts clinicians can bring to MND patients is a clear, systematic approach to the disease. Realising the clinician will methodically address all potential aspects of the disease can bring calm to the patient and loved ones.

Flexibility and adaptability

Another crucial aspect of care is the ability of health professionals to follow the location of the patient. Initially, patients can attend the hospital or private clinics. Eventually, function has deteriorated to the point that patients are effectively house-bound or unable to leave a residential aged care facility (RACF). An MDT, therefore, needs to combine both hospital and home interventions, according to need and circumstance.[47]

Early discussions

The anticipation of, and planning for, complications of MND is an important principle of management. Discussions about the possibility of interventions such as a PEG tube or NIV therapy should be held concurrently and early rather than late. Leaving these discussions too late may mean the patient has progressively lost respiratory function and is no longer fit for an anaesthetic for a PEG tube insertion. Advance care planning is discussed later in this article.

MND support organisations

Finally, clinicians should be aware of the support available through MND associations (national and in each jurisdiction in Australia). Their role is to provide information, support and education for people living with MND, their family, friends and carers. They do this by providing an MND advisory service, MND Infoline, equipment loan, advocacy and by running information sessions for families, carers and health professionals.

The last 12 months: A shift in emphasis

Although it is impossible to be certain when a patient with MND is entering the final 12 months of their life, there is a discernible shift over time in the complexity of their illness and, correspondingly, their needs. In the early phase of the illness, rehabilitation

medicine, in tandem with allied health, comes to the fore, with the goals of maximising function and independence and minimising disability via aids (eg modified cutlery, button fasteners, tap turners), equipment (eg gait aids, orthoses, shower chairs) and building modifications (eg ramps, rails, stair climbers). Allied health therapists can assist with assessment and modifications to the home, car and workplace (occupational therapy), as applicable; speech, swallowing and secretion management (speech pathology); and dietetics to advise on oral intake or PEG feeding. The neurologist monitors symptoms and progression, often initiating referral to other specialists and advising on employment and driving. The respiratory physician investigates and manages progressive respiratory dysfunction, including sleep-disordered breathing. Palliative care is also pivotal at this stage, but with an emphasis on symptom control (eg dyspnoea, sialorrhoea, pain) and future planning (ambulance care plans and advance care directives).

However, the last 12 months often marks a transition in the focus of care, with an ever-diminishing role for the neurologist and rehabilitation physician, and a growing role for palliative care and general practice in managing the panoply of biopsychosocial issues that accompany the end of life (Table 1). This period may also be marked by the need for a transition from home to an RACF, either for respite or permanently, when the needs of the patient exceed the capacity of families and community support services to meet them. This transition can be distressing. Families may feel they have failed the patient. Equally, families, having cared intensely for the patient at home, usually struggle observing the necessarily more limited care provided in an institution, dictated by staffing levels.

A further challenge is the patient aged <65 years who is not readily able, nor perhaps suitable, to enter an RACF. For these patients, the introduction of the National Disability Insurance Scheme (NDIS) has provided greater levels of support in the home. It has enabled the patient to remain in the home setting for longer by aiding the family with much-needed support on many levels (eg direct care workers/equipment/ongoing consumables) as the patient's function deteriorates. Unfortunately, what is lacking for patients aged <65 years is longer-term supported accommodation options other than an RACF, which remains a less than ideal option.

The inequity of service provision to those patients with MND is most striking in those aged >65 years, whose only option for formal support services is via the My Aged Care system. This system remains cumbersome to navigate and sadly lacking in the volume of services needed to assist someone with advanced MND. The lack of comprehensive services available through this system often leads to premature placement in an RACF due to the high burden of care that falls to family members.

Another component of the transition to a palliative pathway is the involvement of community palliative care. The timing of this referral is one of clinical significance. There is no definitive point, but this generally occurs when the needs of a patient are escalating. This referral is made significantly easier if a palliative care health professional has been a member of the MND MDT. Depending on local circumstances, community palliative care can be guided by the MND MDT, including the GP. In a vast country like Australia with regional and remote communities, the GP is often the only health professional guiding both ongoing acute and palliative care. In this situation there may be no access to specialist palliative care or MDT services. The GP may even take on all the roles of the MDT in addition to being a source of strength and courage for the patient and family.

The importance of planning ahead

Multiple and often simultaneous issues arise in the final year of a patient living with MND. Most of these issues are predictable. Rather than simply drifting from one crisis to another without a coherent plan of management, it is extremely important to plan ahead, discuss openly what may happen and allow the patient an opportunity to express their preference on the extent and limits of interventions. Advance care planning is recommended in the international guidelines on MND. Such communication is often delayed, or raised in a crisis situation. An impasse may exist: patients with MND generally welcome the opportunity to discuss end-of-life issues with their doctor;[52] doctors may fear or feel ill-equipped to raise these discussions.[53] The risk of silence is that, in crises, unplanned emergency interventions may occur, up to and including invasive ventilation.[54] The GP is ideally placed to initiate and participate in advance care planning discussions, given their knowledge of the values and perspective of the patient pre-diagnosis.

Modes of death

In what circumstances do MND patients die? Despite commonly held fears, in one large study of MND deaths, choking never occurred.[55] The most common mode of death (85%) is respiratory failure.[55] This may be sudden or more prolonged. In two-thirds of cases, the duration between an acute deterioration and death is less than 24 hours. Respiratory failure can occur even while on NIV therapy. Usually, this period is marked by increasing somnolence, secondary to worsening hypercapnia. Other modes of death include aspiration pneumonia, pulmonary embolism, intercurrent illnesses or elective NIV withdrawal.

Another cause of death in MND patients, in an increasing number of Australian jurisdictions, is voluntary assisted dying (VAD). Coincidental to the subject of this article, under these laws, VAD is permitted for patients with neurodegenerative diseases, such as MND, in the final 12 months of their life. While the laws use precise language, clinicians know how imprecise are the elements of eligibility for VAD as they apply to MND – prognostic uncertainty and altered patient decision-making capacity (especially with varying levels of pre-frontal executive dysfunction and the possibility of undiagnosed depression). Within these laws, it is possible for an MND patient to embark on and

complete the process of VAD without an assessment or management by palliative care, an MND MDT or a psychiatrist. The current VAD laws do not mandate such reviews. As the exact criteria for eligibility and the process of VAD vary across Australian jurisdictions, readers are advised to consult the law as it applies in their jurisdiction.

Care of the dying patient: General principles

In addition to the above, there are general principles that apply to the care of the dying person. These include discussion about location of care, meticulous symptom management, clear and compassionate communication with the family and encouragement for family members to take breaks, sleep and eat through this vigil. In one study of the final month of life, caregivers reported that hospice care improved communication between the medical team and the family, such that there was a better understanding of MND and the goals of care compared to those who did not receive such care.[56]

Bereavement

Given the herculean efforts of families and carers to care for the patient over an extended period, bereavement can be complex. It is important to acknowledge that each loss along the trajectory of the illness (speech, swallowing, mobility, self-care, and so on) brings a form of grief, felt by the patient and family well before the actual death of the patient. Family members become expert carers and may 'second-guess' their actions. GPs have a critical role in bereavement counselling and can refer on where complex bereavement is evident.

Conclusion

MND is an incurable illness with complex manifestations. Over time, it causes significant functional decline, growing levels of dependence and increased carer involvement. These complex needs heighten and accelerate in the last 12 months of life. MND progression should be anticipated and planned for systematically. When available, a multidisciplinary team may be the preferred model to address the protean needs of the MND patient and their family. However, it is crucial to recognise the vital role GPs have in managing patients: pre-diagnosis, managing acute symptoms, palliation and bereavement. The spiritual care the GP brings to the care of a patient and family with MND should be recognised and incorporated into practice and form part of training programs.[57] The Royal Australian College of General Practitioners is an excellent source for training modules and articles relevant to palliative care.

Resources for general practitioners

- MND Australia, www.mndaustralia.org.au
- MND Connect, www.mndaustralia.org.au/mnd-connect/for-health-professionals-service-providers

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