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Factors contributing to delays in the diagnosis of motor neuron disease – A South Australian study

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A B S T R A C T

Objective(s): To characterize the clinical factors that influence time to diagnosis of motor neuron disease (MND) in a cohort of patients living in South Australia.
Design: A retrospective study.
Setting: Single centre study of patients managed at a tertiary referral hospital.
Participants: Patients with MND living in South Australia enrolled in the Australian MND Registry between January 2016 and January 2018. One participant was excluded as study variables of interest were missing.
Results: The mean time to diagnosis was 13 ± 1 months (median 11 months; range 1–38 months) from symptom onset. 41% of patients were classified as having fast disease progression; mean age of disease onset of those with fast disease progression was significantly later in life compared to those with slow disease progression (68 ± 10 years vs 64 ± 8 years) ($P < .05$, $t = -3.921$, df = 220). Patients with fast disease progression were diagnosed significantly earlier than those with slow disease progression (8 ± 1 months vs 16 ± 2 months) ($P < .0001$, $t = 34.6$, df = 220), were less likely to undergo multiple specialist opinions prior to referral to a neurologist (53% vs 73%) ($P < .05$, *Chi-squared* = 9.5, df = 1), and were significantly more disabled at time of diagnosis (mean ALSFRS-R 33 ± 5) than those with slow disease progression (mean ALSFRS-R 41 ± 5) ($P < .0001$, $t = 12.4$, df = 220).
Conclusion(s): Fast disease progression identifies a dichotomy of MND patients that are diagnosed earlier, probable because they are more disabled at diagnosis, likely mediated by a more efficient referral process. A greater awareness of the disease and increased accessibility to neurologists is required to shorten time to diagnosis.

1. Background

Motor neuron disease (MND) is a progressive neurodegenerative disease characterized by death of upper and lower motor neurons, leading to progressive weakness of the bulbar, limb, thoracic and abdominal muscles. Other motor functions, including oculomotor and sphincter function, are relatively preserved, and although there may be sensory symptoms in 20–30% of patients, the sensory examination is usually normal. Cognitive function is impaired in 20–50% of cases, with 15% going on to develop dementia, which is usually frontotemporal in phenotype [1]. The majority of cases are idiopathic, with a small proportion attributable to identifiable single gene mutations. The mean age of onset is 47–52 years in familial disease and 58–63 years in sporadic cases [3]. The lifetime risk of developing MND is 0.2–0.3%, with ageing, male sex, and family history the main risk factors [2–5]. The disease has a fairly stereotypical course, with death from respiratory failure occurring 2–4 years after symptom onset in most cases, though 5–10% patients may survive for a decade or more dependent on the rate of disease progression [2].

Making the diagnosis of MND can be straightforward when there are progressive symptoms of weakness in the bulbar and limb regions, with a combination of upper and lower motor neuron signs, and absence of sensory involvement, thereby fulfilling all clinical criteria for a definite diagnosis based on the currently accepted revised El Escorial and Awaji diagnostic criteria. However, at first presentation, patients rarely have involvement of all regions, and disease progression may be slow and insidious making it difficult to detect subtle changes without serial neurological examination by an experienced examiner [6–8]. More commonly, patients present with symptoms limited to one or two regions, with symptoms that are often non-specific and raise many potential differential diagnoses [6–8], such as multifocal motor neuropathy, Kennedy's disease, myasthenia or a range of myopathies. This leaves patients with either a 'probable', 'possible', or 'suspected' diagnosis of MND and the diagnostic uncertainty that may prevent clinicians from diagnosing such patients, given the grave implications for not only a correct, but an incorrect diagnosis. The introduction of supplementary electrophysiological changes supportive of MND in to current diagnostic criteria have helped increase their sensitivity,

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without decreasing specificity, by detecting subclinical disease [9]; however, suspecting and making a diagnosis of MND still poses a significant challenge for neurologists, but particularly general practitioners, where patients are most likely to first present. Not surprisingly, there is often a significant delay between symptom onset and diagnosis, with a mean time to diagnosis of 10–18 months [10,11]. This has not been well studied, but it is likely that this is multifactorial and attributable to patient, clinician and system factors.

Importantly, early assessment by a neurologist has been associated with a shorter time to MND diagnosis [12]. Given the disease has a short and grave natural history, early diagnosis is vital to optimize outcomes for patients and their families. Early diagnosis reduces the psychological burden of disease without a diagnosis, allows patients and their families to plan their future, reduces unnecessary referral through the health system and minimizes potentially costly and harmful investigations or procedures in search of a diagnosis or treatment of symptoms attributed to an alternative diagnosis [13]. Furthermore, early diagnosis increases the likelihood that a patient will benefit from riluzole, which is currently the only available disease-modifying therapy [14]. In addition to this, early diagnosis facilitates enrolment in clinical trials at an earlier stage of disease, where the likelihood of benefiting from disease-modifying treatment may be greater, and ensures early referral to multidisciplinary clinics, which have been shown to improve survival [15].

Although delay in diagnosis is well documented, there have been no studies that have sought to address this, which may help identify the factors associated with time to diagnosis, enabling targeted implementation of a public health intervention. Using data collected at time of diagnosis and stored in the Australian Motor Neuron Disease Registry, we studied patients diagnosed with MND in South Australia within a two-year period to identify patient characteristics and variables relating to their journey that influence time to diagnosis.

2. Methods

112 patients with motor neuron disease attending the Southern Adelaide MND Clinic based at the Repatriation General Hospital and Flinders Medical Centre enrolled between January 2016 and January 2018 were retrospectively recruited in to a study. One patient was excluded because of missing data. Ethical approval was received from the Southern Adelaide Clinical Human Research Ethics Committee (OFR # 92.18). During clinic review around the time of diagnosis, information pertaining to the patient's demographics and their journey to diagnosis were collected by a specialist physician and stored in the Australian MND Registry. These included: date of first symptom, date of MND diagnosis, sporadic or familial MND, region of symptom onset, clinical signs from which the revised El Escorial classification was determined, amyotrophic lateral sclerosis functional rating scale – revised (ALSFRS-R) score at registration, whether the diagnosis was made by a neurologist or other physician, whether multiple specialist opinions were obtained prior to diagnosis, presence or absence of cognitive impairment, and forced vital capacity at diagnosis. Genetic testing for gene mutations known to cause MND was not performed for all patients and this data was not included in the study. Patients were classified as having fast or slow disease progression, based on progression rate (ΔFS = 48 - ALSFRS-R at diagnosis/disease duration in months) at time of diagnosis [16]. A conservative cutoff of $\Delta FS > 1$ was used to stratify those as having fast disease progression [16]. Data collected in the registry was used to determine whether death occurred in the study period. The means of two samples were compared by a Student's unpaired *t*-test in Microsoft Excel 2008 for Mac (Microsoft, Santa Rosa, CA). Pearson's chi-squared goodness of- fit test was performed to compare the observed and expected frequency distributions in a population in Microsoft Excel 2008 for Mac. Differences were considered significant at $P < .05$.

3. Results

The majority of patients were male (59%) and over the age of 65. The mean age of onset was 66 ± 1 years (range 33–95 years), and was similar between males (65 ± 8 years) and females (67 ± 10 years). Nearly all patients were caucasian (109 of 111) and the majority of patients were living in metropolitan Adelaide (76%), with similar proportions living in outer metropolitan (13%) and rural (11%) areas. Nearly all cases (98%) were sporadic and all but one patient received their diagnosis from a neurologist (one from a general physician). More than two thirds of patients (72%) underwent multiple specialist opinions including from ear nose and throat surgeons, gastroenterologists, orthopaedic surgeons, neurosurgeons and neurologists before being referred to the MND clinic; this amounted to 61%, 68% and 65% of patients with upper limb, lower limb, and bulbar onset of disease, respectively. As per the revised El Escorial criteria for MND, only 4% of patients met criteria for a definite diagnosis. 32% met criteria for probable MND, 37% for possible MND and 7% for suspected MND. 17% did not meet criteria for MND on clinical grounds alone, requiring neurophysiology support to enable the diagnosis. The mean ALSFRS-R scale score at diagnosis was 38 ± 8 (scored out of 48). 41% of patients were classified as having fast disease progression; this phenotype did not have a predilection for gender (51% female), but the mean age of disease onset (68 ± 10 years) was significantly later in life compared to those with slow disease progression (64 ± 8 years) ($P < .05$, $t = -3.921$, df = 220). At time of diagnosis, 8% of all patients had an FVC < 60% and 17% were suspected to have cognitive impairment. 40% of patients died during the study period, the cause of death being attributed to MND in 98% of cases. 55% of deaths were in those with rapid disease progression, with no apparent predilection by region of disease onset (32% lower limb onset, 30% upper limb onset, 32% bulbar onset and 6% multi-region onset).

The mean time to diagnosis was 13 ± 1 months (median 11 months; range 1–38 months) and was not influenced by gender (men: 13 ± 2 months; and women: 13 ± 2 months). There was a wide distribution of time to diagnosis, with some patients diagnosed within months of symptom onset, whilst others were not diagnosed until 3–4 years later. Place of residence in South Australia did not influence time to diagnosis (Table 1). Nearly all patients had symptom onset in a single region (92%), with similar proportions of patients developing onset of symptoms in the upper (33%) or lower limbs (31%) or bulbar region (29%). Rarely, symptoms began in the chest or abdominal wall musculature (4%) or more than one region (4%). The region of symptom onset did not influence the mean time to diagnosis (Table 1) and there was no difference in the mean ALSFRS-R scale score at diagnosis between regions of symptom onset (upper limbs: 38 ± 7; lower

Table 1
Mean time to diagnosis based on patient characteristics.

	Mean time to diagnosis (months ± months)
Location	
Metropolitan	13 ± 1
Outer metropolitan	11 ± 2
Rural	12 ± 1
Region of disease onset	
Upper limbs	12 ± 2
Lower limbs	14 ± 2
Bulbar	12 ± 2
Chest/abdomen	12 ± 7
Rate of disease progression	
Fast disease progression	8 ± 1
Upper limbs	8 ± 2
Lower limbs	8 ± 3
Bulbar	8 ± 2
Slow disease progression	16 ± 2

$N = 111$.

limbs: 37 ± 7; bulbar: 38 ± 7). Fast disease progression disease tended to spare the lower limbs (23% of cases), compared with the upper limbs (37%) or bulbar muscles (33%). Patients with fast disease progression were diagnosed significantly earlier than those with slow disease progression (Table 1) ($P < .0001$, $t = 34.6$, df = 220); this did not appear to depend on region of symptom onset (Table 1). Those with fast disease progression were less likely to undergo multiple specialist opinions prior to referral to a neurologist (53% vs 73%) ($P < .05$, *Chi-squared* = 9.5, df = 1). In addition, patients with fast disease progression were significantly more disabled at time of diagnosis (mean ALSFRS-R 33 ± 5) than those with slow disease progression (mean ALSFRS-R 41 ± 5) ($P < .0001$, $t = 12.4$, df = 220).

4. Discussion

MND is a progressive neurodegenerative disease with management focused largely around supportive care of complications. There is currently no established biomarker available in clinical practice, making diagnosis a significant challenge. The rate of disease progression is predictive of survival, and therefore carries prognostic significance [16]. Riluzole is the only medication available in Australia that slows disease progression, with strict criteria for prescription that restricts its use to early stage disease. Non-invasive ventilation for patients with respiratory failure improves survival and quality of life [17,18]; gastrostomy improves quality of life, but it is unclear if it confers a survival benefit [19]. There is compelling evidence that patients who attend a multidisciplinary clinic have an improved quality of life and survival [15]. Timely diagnosis facilitates early referral to a multidisciplinary clinic and access to these services. This is the first study attempting to characterize potential barriers to making a diagnosis of MND in patients living with the disease in Australia.

There is often a considerable delay between developing symptoms and being diagnosed with MND. Our study of patients in South Australia confirmed this, and demonstrated a similar, though slightly shorter, delay to that reported in other developed countries [20]. There was no difference in the time to diagnosis based on the region of disease onset, as patients with spinal-onset disease experienced similar delays to those with bulbar-onset disease. This is in contrast to a previous report in the literature of patients with bulbar-onset disease being diagnosed, on average, 4 months earlier than those with spinal-onset disease [13]. The mechanism underlying this observation is not clear, as the authors' reported no difference in bulbar- and spinal-onset patients in terms of the likelihood of being referred from a general practitioner to a neurologist, nor in the likelihood of attending a neurologist within the first three initial consultations with a health care practitioner [13]. The cohort of patients in this study differed from ours, with more than two thirds having spinal-onset disease [13]. There is no intrinsic reason to suspect that those with bulbar-onset versus lower-limb onset should be diagnosed any earlier, as both pose a broad set of differential diagnoses, and in our study, we did not observe a difference in the proportion of patients with rapid and slow disease progression based on the region of disease onset.

At disease onset, the majority of patients had symptoms confined to a single region, and even at the time of first MND clinic review, most commonly only 1 or 2 regions were affected. As a consequence, < 5% of patients met definite criteria for diagnosis of MND, as per the revised El Escorial criteria. Approximately two thirds of patients met 'probable' or 'possible' criteria; the remaining third met 'suspected' criteria, or were supplemented by supportive neurophysiological changes, without which many would not meet criteria for diagnosis on clinical grounds alone [21]. In our experience, these neurophysiological changes 'upstage' diagnosis in an estimated 30% of cases. These observations highlight the current challenges in making a diagnosis of MND. Firstly, a high index of clinical suspicion is required, especially amongst clinicians inexperienced in MND. This lack of familiarity likely contributes substantially to the delay in diagnosis that occurs in the primary care setting. Secondly, even with strong clinical suspicion, there is often a paucity of evidence to support a diagnosis with a considerable degree of certainty. This likely contributes to the delay in diagnosis that occurs following referral to a neurologist. Increased awareness of MND in the community would partially help address the delay in presentation that occurs in primary care. Improved clinical awareness would lead to a reduction in inappropriate referrals to specialists other than a neurologist, unnecessary investigations and procedures, and more timely referral for neurophysiological studies. Although a candidate biomarker for MND exists [22], its current use remains as a research tool to monitor progression for patients that already meet the clinical criteria for diagnosis. At present, no diagnostic biomarker exists, the diagnosis being made on clinical grounds after exclusion of potential mimics.

We observed that patients with fast disease progression are diagnosed earlier than those with slow disease progression. This is not surprising, as more rapidly progressive symptoms are less likely to be ignored or go unnoticed by patients, prompting earlier presentation to their primary care providers, who are more likely to detect "red flag" symptoms and refer for specialist opinion earlier [23]. This is supported by our observation that those with fast disease progression are less likely than those with slow disease progression to undergo multiple specialist opinions prior to referral to a neurologist, suggesting rate of disease progression influences recognition of the patient's presentation being due to a neurological condition, such as MND.

Patients with fast disease progression were also more disabled than those with slow disease progression at time of first presentation to the MND clinic. Although they are less likely to be subjected to an inefficient referral process compared to those with slow disease progression, significant deterioration while awaiting assessment by a neurologist once a referral remains a possibility. The waiting times to see a neurologist in South Australia are unacceptably long in both private and public, with a wait of longer than 12 months common in private and longer in public for patients with non-urgent problems. The information provided in the referral is critical to accurately triage patients, as if there is a high clinical suspicion of MND on the referral information provided, a patient would be likely to be seen within a month in private and 3–6 months in public. Once diagnosed and referred to the MND clinic, patients are usually seen within 1 month.

5. Conclusion

The time to diagnosis of MND is similar in Australia compared to other parts of the developed world. Although multiple regions are inevitably affected, symptoms typically begin in one region, and clinicians always need to consider MND when a single region has been afflicted. In primary care, an increased awareness of MND, careful serial neurological examination, and when the index of suspicion is high, neurophysiological studies are essential to recognise the disease and its characteristic progression and increase the likelihood of a timely diagnosis. Limitations with the current clinical diagnostic criteria and absence of a diagnostic biomarker unfortunately can still delay diagnosis once a patient has been referred to a neurologist. For most patients, the journey to diagnosis is inefficient, with referral to a specialist other than a neurologist resulting in unnecessary investigations and procedures, delaying the diagnosis. Fast disease progression identifies a dichotomy of patients that are diagnosed faster, which may be mediated by earlier accrual of disability and more efficient referral to a neurologist. However, these patients are more disabled at the time of diagnosis, which may prevent them from accessing riluzole and timely referral to multidisciplinary clinics, which improve survival, or enrolling in clinical trials of experimental disease-modifying agents. An improved awareness of MND in the community amongst patients, allied health and clinicians, and timely access to neurologists mediated by high quality referrals will result in immediate improvements in the delay to diagnosis and improvements in patient outcomes.

Author contribution

DFS and DWS designed the study; DFS and DWS collected the data; DFS analysed the data; DFS and DWS wrote the manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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