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Specialist referrals and diagnostic delays in motor neurone disease: Mapping patients' journey through hoops and hurdles in healthcare

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ABSTRACT

Motor neuron disease (MND) is an uncommon but invariably fatal condition, with a median survival of 24–48 months from symptom onset. Although there is no cure at the moment, early diagnosis is crucial to enable timely access to multidisciplinary care, and enrolment in clinical trials utilising investigational therapies. Unfortunately, diagnostic delays remain common, and the average delay between symptom onset and diagnosis is 12 months. Large numbers of specialist referrals have been suggested as a key contributor to diagnostic delays.

We conducted a retrospective review of the medical records of patients diagnosed with MND in Lancashire and South Cumbria, to investigate whether large numbers of specialty referrals are a common occurrence in MND.

Our review identified that 35% of patients with MND were seen by two or more specialties before being referred to neurology. This rose to 49% when patients with bulbar onset disease were considered. 9% of cases saw three or more specialists. There was a statistically significant correlation between the number of specialist referrals and delays in neurology referral. We hope our findings will increase awareness of the importance of early neurology referral in the diagnosis of MND and promote the use of the MND Red Flag tool as a means of identifying patients in need of prompt neurological evaluation.

Introduction

Motor neuron disease (MND) is an incurable and relentlessly progressive neurodegenerative disease resulting in loss of motor neurons. The annual incidence is approximately 2/100,000 while the prevalence is 5–7/100,000.[1] The peak incidence occurs between 60–75 years of age with a male to female ratio of 1.3 to 1.5.[1] While MND is a largely sporadic illness, around 5–10% of cases are familial and tend to have a younger onset.[2]

MND is a heterogenous disorder; the site of onset, rate of progression, and degree of upper and lower motor neuron involvement vary enormously between individuals. Three main patterns of disease onset have been recognised: limb onset, commonly presenting with asymmetric limb weakness; bulbar onset, presenting primarily with speech and swallowing problems; and respiratory onset, presenting with respiratory insufficiency.[3]

Life expectancy in amyotrophic lateral sclerosis (ALS), the most common form of MND, is 2–5 years from the onset of symptoms. In the absence of a cure, management is largely symptomatic, although treatment with the neuroprotective drug, Riluzole, has been shown to provide a modest survival benefit.[4-5] NIV, where indicated, also improves survival and quality of life.[6]

A worldwide research effort to develop effective treatments for MND is underway, with a number of institutions and pharmaceutical companies being actively engaged in drug development. In 2022, the UK government pledged £50 million towards MND research as part of this drive, and this has led to the establishment of the UK MND Research Institute (UK MND RI), resulting in several collaborations between universities, charities, and life science organisations. The UK MND RI has the vision of 'accelerating drug discovery from laboratory science to phase 3 clinical trials, to make MND a curable condition'.

There is emerging evidence that MND is characterised by a presymptomatic period in which neuronal loss has already started. Identifying patients at an early stage may provide opportunities to modify the course of illness with investigational drugs. A number of clinical trials, some aimed at developing pioneering gene therapies and disease modifying treatments, are in the pipeline. There are already promising results, and Tofersen, the gene therapy for treatment of MND associated with pathogenic SOD1 gene variants, has been shown to slow disease progression, with more pronounced benefits in those starting treat-

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ment earlier.[7] Similarly, an ongoing phase 3 clinical trial called ATLAS is investigating the use of Tofersen in pre-symptomatic carriers of SOD1 gene mutations.[8] This highlights the importance of early diagnosis to enable timely genetic testing and provide access to experimental genetic therapies.

Early diagnosis of MND is therefore becoming increasingly important; not only does it reduce the distress associated with diagnostic uncertainly and multiple investigations, but also facilitates timely enrolment into the ever-expanding number of clinical trials. Timely diagnosis offers patients the time to come to terms with their condition, empowers them to make decisions about their treatment options, and consider advance care planning, including financial, psychosocial and existential aspects. Similarly, early diagnosis can improve quality of care through early access to multidisciplinary teams, which have been demonstrated to have a positive impact, not only on survival and quality of life but also on limiting unnecessary interventions and the overall cost of care.[9]

Unfortunately, diagnostic delay of around 12 months between symptom onset and diagnosis is a common problem.[10-13] Despite this delay remaining stubbornly persistent, few studies have explored the reasons for this. Large numbers of specialist referrals have been suggested as an important factor.[12-13]

We investigated whether referrals to non-neurologists contributed to delays in diagnosis for patients presenting with MND. We recorded the number of non-neurological specialist referrals made for patients with MND presenting to a tertiary referral centre and whether this differed according to their presenting symptoms.

The MND Red Flag tool, taken from the resource 'Motor Neurone Disease: a guide for GPs and primary care teams', published by the Motor Neurone Disease Association (MNDA) and the Royal College of General Practitioners (RCGP), is a simple diagnostic aid alerting clinicians to the possibility of MND and the need for early neurological referral. We believe that wider adoption of the tool could promote earlier referral of patients with suspected MND, and help reduce diagnostic delays. The data published herein is envisaged as the first part of a quality improvement project seeking to promote use of the MND Red Flag tool to expedite neurological referral and diagnosis within our catchment area.

Methods

We conducted a retrospective review of the electronic medical records of all patients residing in Lancashire and South Cumbria who were diagnosed with MND over a 5-year period (2016–2021). We reviewed hospital correspondence, clinic letters, inpatient notes, investigations, discharge summaries and electronic GP records, where accessible.

Approval for service evaluation was obtained from the Clinical Audit and Improvement Department, Lancashire Teachings Hospitals NHS Foundation Trust. Data regarding the date of onset, initial symptoms, age at onset, site of onset, date of neurology referral, date of diagnosis, date of death (if applicable) and syndromic diagnosis were recorded. Information about the number and type of non-neurological secondary care referrals was also recorded. The outcome of such appointments in terms of investigations and further referrals was documented. We cross-referenced all data between sources to ensure accuracy.

The records for 181 cases were reviewed. The primary outcome measure was the type and number of non-neurological specialty referrals made prior to the diagnosis of MND. The number of investigations each patient underwent prior to being referred to neurology and the number of days from first presentation to neurological referral was also recorded.

The relationship between number of referrals and time to neurological referral was analysed using the Mann–Whitney U test for non-parametric data. The time difference between direct referral to a neurologist and any number of non-neurological referrals was analysed. Patients with more than two referrals were also compared to those with less than two referrals.

Primary outcome data was available for 103 patients (56.9%). Patients in whom primary outcome data was not available were excluded from the analysis. Other exclusion criteria included patients diagnosed privately; patients diagnosed out-of-area; patients whose neurology referrals were untraceable, and patients who developed MND while already under the care of a neurologist.

Results

Patient characteristics

A total of 55 cases were male (53.4%) and 48 were female (46.6%). Their baseline characteristics are summarised in Table 1. Median age of symptom onset was 69 years; 65 years for males, and 70 years for females. 62 patients (60%) had limb-onset symptoms, while 39 patients (38%) had bulbar-onset disease. One patient presented with respiratory failure and one patient presented with cognitive symptoms (Fig. 1).

Of the limb-onset patients, 10 presented with arm weakness (16%); 14 presented with hand weakness (23%) and 28 presented with leg weakness, altered gait, and falls (45%). Six patients presented with foot drop (10%). Two patients presented with hemiparesis or generalised weakness (3%). One patient presented with fasciculations (2%).

Of 39 patients with bulbar-onset MND, 18 presented with dysarthria (46%), eight with dysphagia (21%), and 12 patients (31%) presented with both. One patient presented with cognitive impairment and one patient presented with breathlessness (1%, respectively). The presenting symptoms for two patients were not identifiable.

Specialist referrals in MND

The mean number of specialty consultations prior to neurology referral was 1.23 for all patients. Patients with bulbar-onset symptoms had a mean of 1.44 specialty consultations prior to neurology referral. The mean figure for those with limb-onset was 1.1. The mean number of investigations performed prior to neurology referral was 1.49 for all patients. This rose to 1.63 for patients with bulbar-onset symptoms, but fell to 1.27 for patients with limb-onset disease.

19 patients (49%) with bulbar-onset disease saw two or more specialists before being referred to a neurologist (Fig. 2). 15 patients (38%) were seen by two specialists. Three patients (8%) were seen by three specialists and one patient (3%) was seen by four specialists. Seven patients (18%) were referred directly to neurology while 13 (33%) were seen by one specialist prior to neurology referral.

16 patients (26%) with limb-onset disease saw two or more specialists prior to neurology referral. 11 (18%) saw two specialists, two (3%) saw three specialists, and three (5%) saw four specialists. 18 patients (29%) were referred directly to neurology while 28 patients (45%) saw one specialist prior to neurology referral.

In total, 36 patients (35%) were referred to two or more specialists prior to neurology referral. 27 patients (26%) saw two specialists, five patients (5%) saw three specialists, and four patients (4%) saw four specialists. 25 patients were referred directly to neurology (24%), while 42 patients (41%) saw one specialist before neurology referral.

Referral destinations for patients with bulbar and limb onset MND are summarised in Tables 2 and 3. ENT was the most common referral destination for patients with bulbar onset MND (67% referred). This rose to 100% when patients with isolated dysphagia were considered (Fig. 3). 75% of patients with dysarthria and dysphagia were referred to ENT. 18% of patients with bulbar-onset MND were referred to stroke, 13% were referred to upper GI surgery and 8% were referred to gastroenterology. 20% were referred to SALT, often as a last resort. Other destinations included elderly medicine, respiratory medicine, and the emergency department. One patient was referred to orthopaedic surgery following two separate reviews by upper GI surgery and one by ENT. One patient was referred to breast surgery.

Table 1
Patient demographic and clinical characteristics.

Variable	Characteristic	Frequency (*N*=103)	Percentage (%)
Sex	Male	55	53
	Female	48	47
Site of onset	Bulbar	39	38
	Limb	62	60
	Respiratory	1	1
	Cognitive	1	1
Symptoms at onset	Dysarthria	18	17
	Dysphagia	8	8
	Dysarthria and dysphagia	12	12
	Dyspnoea	1	1
	Arm weakness	10	10
	Fasciculations	1	1
	Foot drop	6	6
	Hand weakness	14	14
	Hemiparesis/general weakness	2	2
	Leg weakness, altered gait & falls	28	27
	Cognitive impairment	1	1
	No data	2	2

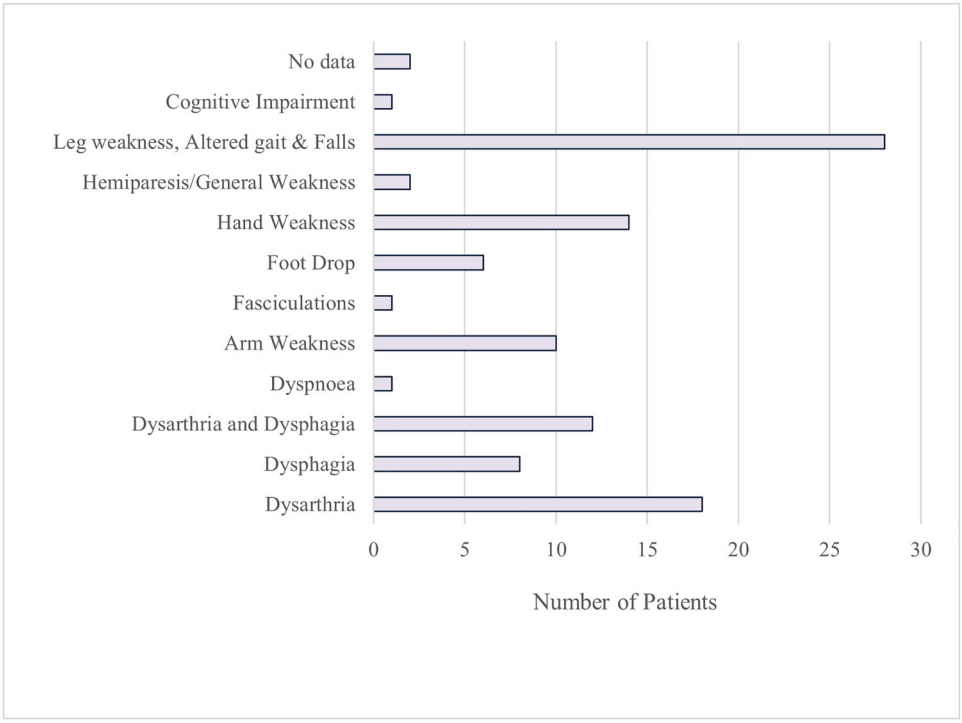

Fig. 1. Presenting symptoms of patients included in the study.

Table 2
Bulbar onset MND - number of specialty referrals by site and symptoms at onset (percentage of patients referred to each specialty are shown in brackets).

Specialty	All bulbar onset (*N*=39)	Dysarthria (*N*=18)	Dysphagia (*N*=8)	Dysarthria & dysphagia (*N*=12)	No data (*N*=1)
ENT	26 (67%)	8 (44%)	8 (100%)	9 (75%)	1 (100%)
Stroke	7 (18%)	5 (28%)	0	2 (17%)	0
Upper GI surgery	5 (13%)	1 (6%)	3 (8%)	1 (8%)	0
Gastroenterology	3 (8%)	0	3 (38%)	0	0
Elderly medicine	1 (3%)	0	0	1 (8%)	0
Emergency medicine	1 (3%)	1 (6%)	0	0	0
Respiratory	3 (8%)	3 (17%)	0	0	0
SALT	8 (20%)	4 (22%)	1 (13%)	2 (17%)	1 (100%)
Breast	1 (3%)	0	0	1 (8%)	0
Orthopaedics	1 (3%)	0	1 (13%)	0	0
Total referrals	**56**	**22**	**16**	**16**	**2**

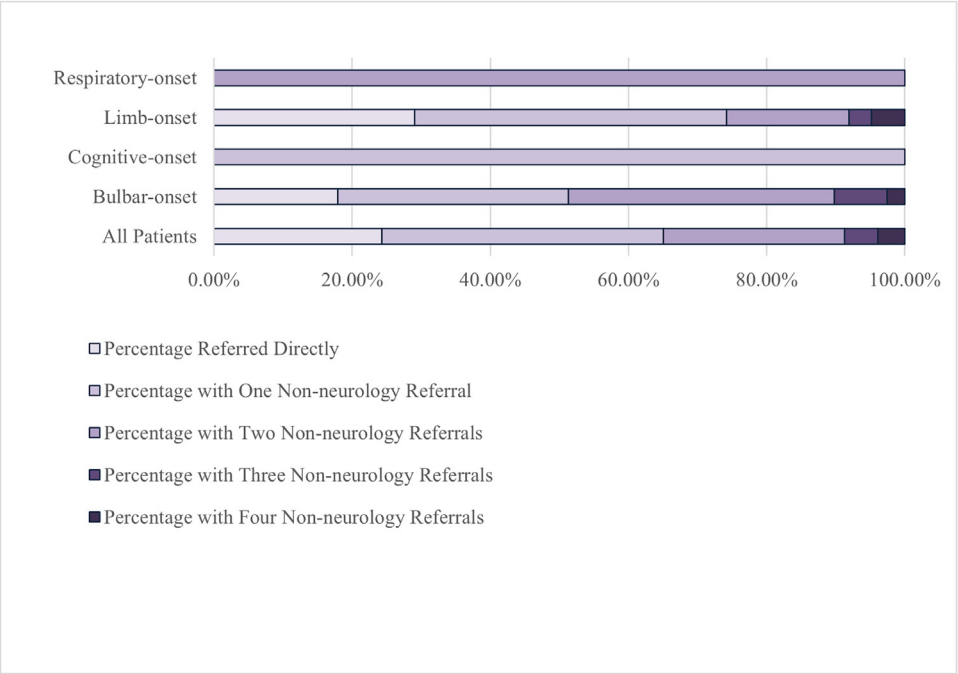

Fig. 2. Number of non-neurology specialist referrals by site of disease onset.

Table 3
Limb onset MND - number of specialty referrals by site and symptoms at onset (percentage of patients referred to each specialty are shown in brackets).

Specialty	All limb onset (*N*=62)	Arm weakness (*N*=10)	Hand weakness (*N*=14)	Leg weakness, altered gait & falls (*N*=28)	Foot drop (*N*=6)	Hemiparesis/eneral weakness (*N*=2)	Fasciculations (*N*=1)	No data (*N*=1)
Neurosurgery	13 (21%)	2 (20%)	4 (29%)	6 (21%)	1 (17%)	0	0	0
Orthopaedics	13 (21%)	1 (10%)	4 (29%)	7 (25%)	1 (17%)	0	0	0
Musculoskeletal medicine	8 (13%)	0	5 (36%)	1 (4%)	2 (33%)	0	0	0
Stroke	9 (15%)	4 (40%)	2 (14%)	2 (7%)	0	1 (50%)	0	0
General medicine	6 (10%)	0	1 (7%)	4 (14%)	0	0	1 (100%)	0
Rheumatology	2 (3%)	2 (20 %)	0	0	0	0	0	0
Elderly medicine	6 (10%)	2 (20%)	0	4 (14%)	0	0	0	0
Emergency medicine	1 (2%)	0	0	1 (4%)	0	0	0	0
Hand surgery	1 (2%)	0	1 (7%)	0	0	0	0	0
ENT	3 (5%)	0	0	3 (11%)	0	0	0	0
Upper GI surgery	1 (2%)	0	0	1 (4%)	0	0	0	0
Physiotherapy	4 (6%)	1 (10%)	0	2 (7%)	1 (17%)	0	0	0
SALT	1 (2%)	0	0	1 (4%)	0	0	0	0
Total referrals	**68**	**12**	**17**	**32**	**5**	**1**	**1**	**0**

Patients with limb-onset MND were most likely to be referred to neurosurgery and orthopaedics (21%, respectively), followed by stroke (15%), and musculoskeletal medicine (13%). Other referral destinations included general medicine, elderly medicine and rheumatology (Fig. 4). 6% of patients were referred to physiotherapy. Three patients (5%) were referred to ENT, while upper GI surgery and SALT each received one referral, heralding the subsequent onset bulbar symptoms. All but one of these patients had previously been by neurosurgery, elderly medicine, and stroke with initial complaints of leg weakness. The final patient presented with fasciculations but was referred to ENT at an early stage.

Delays in neurological referral

The mean duration from first presentation to neurology referral was 173 days (Fig. 5). For patients referred directly to neurology, the wait for neurology referral was 19 days (range 73, SD 23.7). The mean interval to neurology referral for patients who saw one or two non-neurology specialists was 229 days (range 1,389, SD 307.48), and 212 days (range 419, SD 162.3), respectively. Patients who saw three specialists waited 440 days for neurology referral (range 27, SD 13.5). Data on referral times were only complete for one patient who saw four different specialists. Neurology referral in his case occurred 483 days after presentation. Patients with bulbar-onset disease waited an average of 214 days for neurology referral after first presentation, while those with limb-onset disease waited an average of 148 days.

Statistical analyses revealed significant differences in the wait for neurology referral between those referred directly and those who saw one specialist or more (Z score 4.79001, p-value < 0.00001). The wait for neurology referral was also significantly shorter for patients who saw one specialist or less than for those who saw two specialists or more (Z score -3.00596, p-value 0.00131).

Discussion

Early diagnosis of MND is becoming increasingly important. Unfortunately, diagnosis is often delayed, and an interval of 12 months be-

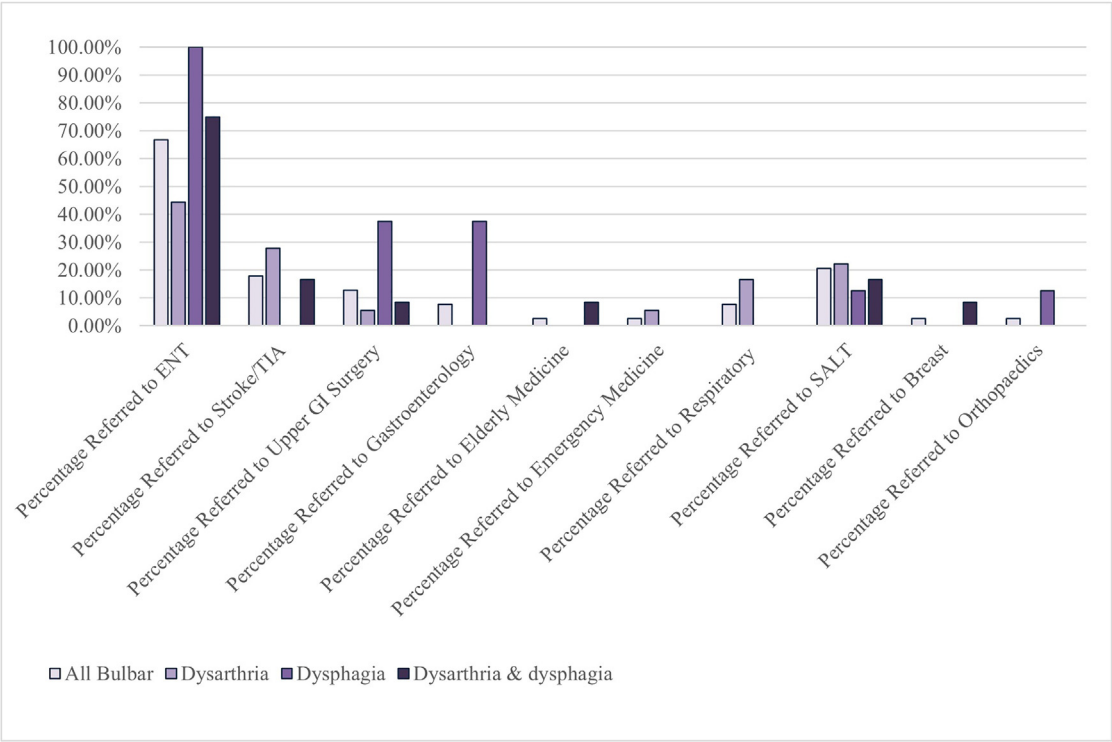

Fig. 3. Proportion of patients with bulbar-onset MND referred to specialties other than neurology organised by presenting symptom.

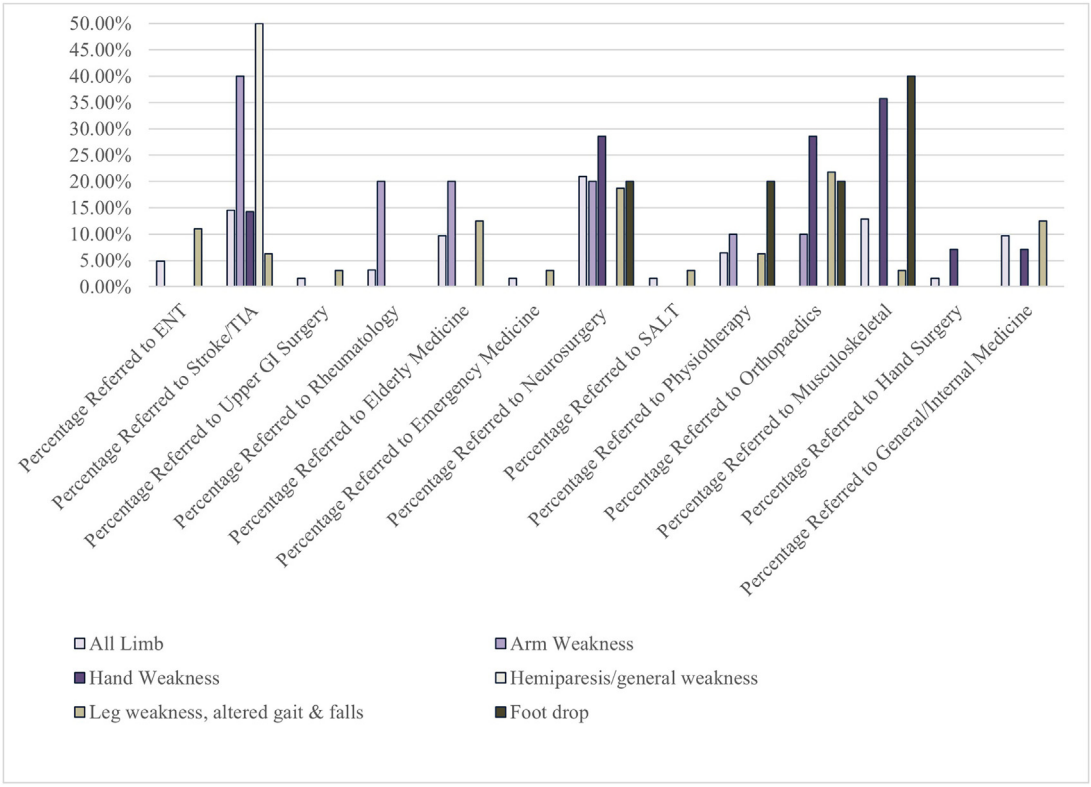

Fig. 4. Proportion of patients with limb-onset MND referred to specialties other than neurology organised by presenting symptom.

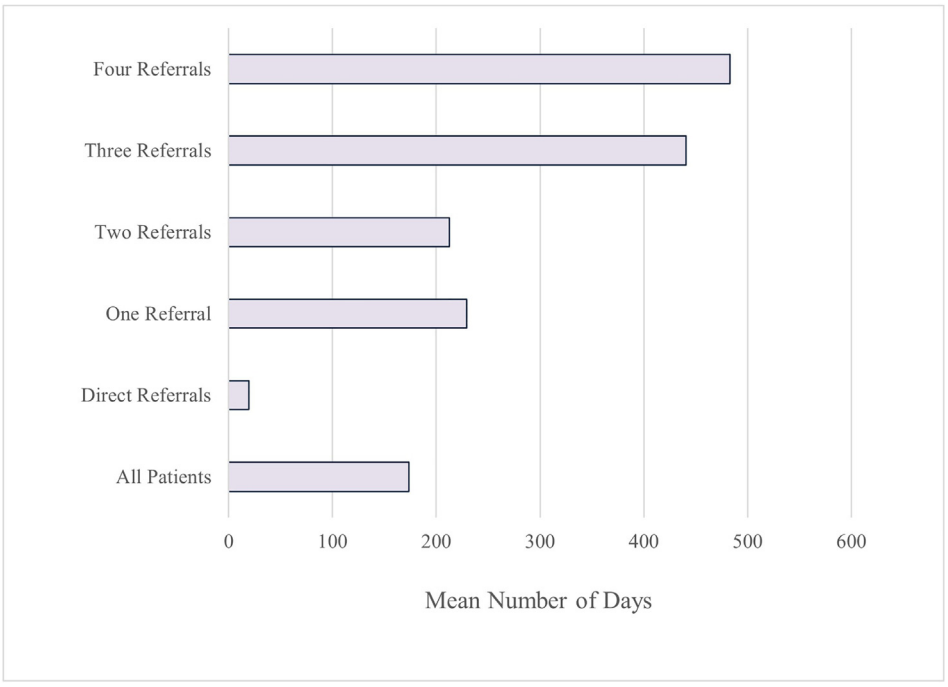

Fig. 5. Mean number of days from presentation to neurology referral according to number of non-neurological specialist referrals.

tween first presentation and diagnosis is consistently reported in the literature.[10-13] These delays have been attributed to a number of factors, including referrals to non-neurologists.[12-13]

Our data confirm that referrals to non-neurologists are a frequent occurrence in MND. 75% of patients with MND were initially referred to a non-neurologist. 35% of patients were seen by two or more specialists prior to neurological referral; rising to 49% for those with bulbar onset symptoms. 9% of patients were referred to three or four different departments before a neurology opinion was requested.

Patients with bulbar-onset symptoms were at particular risk of referral delays. 75% of patients with dysarthria and dysphagia were referred to ENT. This rose to 100% of patients presenting chiefly with dysphagia, while 44% of patients presenting with isolated dysarthria were also referred to ENT. Dysarthria is a motor speech disorder, the presence of which points towards neurological, rather than surgical pathology. It is usually the first sign of bulbar-onset MND, with dysphagia occurring later in the course of the illness. The high frequency of ENT referrals in patients with bulbar-onset MND indicates a lack of cognisance amongst clinicians about MND as a potential cause of these symptoms. Indeed, in several bulbar-onset cases, neurology referral was suggested by speech and language therapists after other medical avenues had been exhausted. In one notable case, a patient underwent three separate OGDs following two referrals to upper GI surgery before being referred to ENT. The same patient was subsequently referred to orthopaedic surgery, indicating that the subsequent onset limb weakness in a patient with speech and swallowing problems was insufficient to prompt consideration of a neurological diagnosis.

Similarly, several patients with limb symptoms were referred to ENT following the onset of bulbar dysfunction without the possibility of MND being considered. While patients presenting with limb symptoms saw fewer non-neurologists than those with bulbar-onset disease, only 29% were referred directly to neurology. A total of 49% of patients were referred to either orthopaedics, stroke, or musculoskeletal medicine, again indicating a lack of awareness that painless, progressive weakness is most likely to indicate neurological pathology.

Our also shows that increased number of non-specialty neurology referrals is associated with greater time to neurology referral, which exacerbates diagnostic delay. Statistical analysis showed that even a single referral to a non-neurologist leads to a significant delay in neurological referral. Subsequent non-neurology referrals lead to further significant delays in time to neurology referral.

Conclusion

This study demonstrates that a significant proportion of patients presenting with symptoms of MND are initially referred to specialties other than neurology, leading to delays in neurology referral. Timely referral to neurology would not only improve the patient's diagnostic journey, reduce distress associated with uncertainty and multiple investigations, but also empower patients to communicate their individual values, preferences, and care priorities, including those pertinent to advance care planning.

While there is no cure for MND, several promising treatments are on the horizon. Tofersen, the first disease-modifying treatment for MND, has already been granted marketing authorisation by the European Commission and is currently being evaluated by NICE. Given the expanding number of investigational therapies, including experimental gene therapies, early diagnosis is more crucial than ever in allowing patients to enrol in these trials, many of which are modelled to detect treatment effects in the early stages of the illness. A significant proportion of motor neurones are lost by the time of symptomatic presentation and earlier diagnosis may provide a window of opportunity to preserve the remaining motor neurons and forestall disease progression. As a consequence, diagnostic delays may not only be associated with limited/delayed access to multidisciplinary care and reduced quality of life,[9] but also hinder research and the promise of potentially effective treatments for MND. MND is a relentlessly progression condition, and as the Tofersen data demonstrates, the earlier treatment can be started, the better.

The MND Red Flag tool presented in 'Motor Neurone Disease: a guide for GPs and primary care teams' by the MNDA and RCGP is a simple aide memoir to help prompt primary care physicians to consider MND as a possible diagnosis, with the aim of securing early neurological referral and reducing diagnostic delays. We hope this paper will draw attention to the issue of diagnostic delays in MND and raise awareness of the value of the MND association Red Flag tool in identifying patients in need of urgent neurological referral. The data will also form the basis of a focused approach to promote awareness of the MND Reg Flag tool, including through educational sessions, in our catchment area.

Author contributions

Dr Samuel James Reynolds – Methodology, Data curation, Formal analysis, Writing - original draft.

Prof Suresh Kumar Chhetri – Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare there is no conflict of interests.

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