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Demographics, characteristics, and clinical profile of motor neuron disease in oman

Abstract

Background: Motor neuron disease (MND) presents a considerable health challenge globally and is characterized by progressive neurodegeneration leading to debilitating weakness and eventual respiratory failure. Despite its impact, studies on MND from the Middle East and North Africa region are scarce. Considering the seriousness of the disease, it is important to recognize the demographics, clinical spectrum, and heterogeneity of MND cases to enable early diagnosis and the prompt initiation of supportive interventions to improve survival, quality of life, and physical functioning as there are presently no therapies to arrest or reverse this fatal disease.

Objective: This study aimed to elucidate the demographics, clinical characteristics, management strategies, and outcomes of MND in Omani patients admitted and/or referred to a single tertiary care hospital in Muscat, Oman.

Methods: A total of 29 patients diagnosed with MND who were treated and followed up at the neuromuscular disorders clinic, Khoula Hospital, Muscat, Oman, between January 2016 and April 2020 were retrospectively reviewed. Data collection and analysis included patient demographics, site of onset, duration of symptoms, clinical features, and the results of diagnostic workup. The initial primary diagnosis, clinical course follow-up, and treatments and supportive interventions were also reviewed. Furthermore, outcome measures and survival were recorded.

Results: The patients had a male-to-female ratio of 1.23:1, a mean age of symptom onset of 54.7±12.7 years, and a mean duration of the disease from its onset to diagnosis of 20.3±20.9 months. Most patients (69%) presented with significant limb muscle weakness at diagnosis, with an overall revised amyotrophic lateral sclerosis functional rating scale of 35.14±10.49. MND was considered initially in 21% of the cases, while the most common primary diagnoses were cervical and lumbosacral radiculopathy (in 34% of the cases). The classic amyotrophic lateral sclerosis of spinal onset (cervical and lumbar) was the most common clinical phenotype (in 41.4% of the studied patients). The mean duration of follow-up was 48 months, and by the end of the study, 27.6% of the patients with MND were on mechanical ventilation (invasive and noninvasive), 34.5% had parenteral tube feeding, and 86% were on treatment with riluzole. Survival analysis revealed gender-related differences, with females exhibiting shorter survival times than males (26 vs. 42 months).

Conclusion: As a novel, comprehensive report on the Omani MND population, this study revealed that the epidemiological and clinical characteristics of the disease in Oman were similar to those observed in international populations. However, our study indicated a higher survival rate because of the early initiation of supportive interventions. In addition, this study showed that Omani women had a longer duration of diagnostic delay and a shorter median survival time than men. We suggest a longer-term (5–10 year follow-up) multicenter study involving local and regional centers to include a larger number of patients with MND for obtaining a better understanding of the disease in this region.

Keywords: motor neuron disease; amyotrophic lateral sclerosis, clinical phenotypes, oman

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Introduction

Motor neuron disease (MND) is a neurodegenerative disease characterized by the progressive loss of upper motor neurons (UMNs) and lower motor neurons (LMNs) throughout the central nervous system, leading to progressive weakness of the bulbar, limb, thoracic, and abdominal muscles.[1] This condition can be sporadic (in 90%–95% of cases) or hereditary[2] and encompasses a group of heterogeneous clinical presentations of rapidly progressive and universally fatal disorders with variability in disease progression and survival.[3] Therefore, the diagnosis and classification/categorization of MND are based on a defined set of diagnostic criteria (the revised El Escorial and the Awaji criteria).[4–6]

The varied clinical presentations of MND include the following: (i) Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease, is the comment phenotype. It starts with limb weakness (spinal onset) and progressive neurological deterioration with the coexistence of UMN and LMN signs. (ii) Progressive muscular atrophy (PMA), representing approximately 10% of MND cases, is a clinically pure LMN phenotype. (iii) Primary lateral sclerosis (PLS), constituting 1%–5% of MND cases, is a clinically pure UMN phenotype. (iv) Isolated progressive bulbar palsy (PBP), present in 1%–2% of MND cases, causes an isolated bulbar phenotype with relative preservation of spinal motor neurons.[3,7]

PMA, the clinically atypical MND phenotype, includes the flail-limb variants characterized by neurogenic weakness confined to the proximal upper limbs (flail-arm) for at least 24 months or confined to the lower limbs (flail-leg) for at least 12 months.[8,9] One-third of PMA cases may develop UMN dysfunction.[9] PLS (with pure UMN

involvement) and PMA (with pure LMN involvement) are rare, and certain patients initially classified into these subtypes can evolve into ALS.[10] More recently, an association has been established between ALS and frontotemporal degeneration.[11] Despite the clinical heterogeneity, the median survival of patients with MND remains approximately 3 years, although the atypical phenotypes exhibit a favorable longer survival.[12]

Being a relatively rare disease with varied presentations and progression, patients with MND are often diagnosed late after manifesting their initial symptoms, with a reported median time to diagnosis of approximately 14 months.[13] Although a combination of UMN and LMN signs and symptoms in a patient should raise the clinical suspicion of MND, other conditions can also present with both UMN and LMN signs and symptoms, making many cases of MND misdiagnosed. In contrast, some potentially treatable conditions may be diagnosed as MND. A population-based study has reported an overall 10% error in the diagnosis of ALS.[14]

Once the diagnosis is confirmed, MND is invariably a fatal condition, and the main cause of death is respiratory failure. However, early diagnosis has been shown to play a pertinent role in extending the life expectancy of patients.[15]

In addition, the use of noninvasive ventilation (NIV) in patients with severe respiratory muscle involvement, placement of a feeding gastrostomy tube, and treatment with riluzole can prolong survival.[6,16] The overall global incidence of ALS has been estimated to be between 0.6 and 3.8 per 100,000 person-years, with wide variations among geographical regions.[17–20] A probable explanation for this observation is a combination of genetic, environmental, and lifestyle factors.[18,20]

There is a paucity of literature from the Middle East and North Africa region on MND. A consanguineous family from Saudi Arabia with juvenile ALS in an autosomal recessive pattern has been reported, and the responsible gene has been identified.[21] In a retrospective study from six neurology departments in Iran, a crude prevalence of 1.57/100,000 for ALS has been identified.[22] Furthermore, an average incidence of 0.89/100,000 and a prevalence of 3.47/100,000 have been documented in Libya,[23] with a median survival time of 42 months. A study from Tunisia has described a case series of 60 patients with ALS with an average age of 52.1±11.2 years.[24] There is a lack of literature on this rare but serious and fatal disease from the Sultanate of Oman. This single-center study discusses the clinical characteristics and follow-up of a cohort of ethnic Omani patients with MND.

Subjects and methods

This research was a retrospective, descriptive, single-center study involving patients diagnosed with MND based on the El Escorial and Awaji-Shima criteria.[4,6] during March 2016–April 2020 at the neuromuscular disorders clinic in a tertiary center at Khoula Hospital, Muscat, Oman. The inclusion criteria were a diagnosis of MND by a neurologist after eliminating other similar diseases and meeting the revised El Escorial and Awaji-Shima criteria for definite MND in adult patients. Those with other forms of anterior horn cell disease and motor axonal neuron disease who did not fulfill the revised El Escorial and Awaji-Shima diagnostic criteria, those with other MND mimickers, and those with an alternative diagnosis were excluded.

Demographic characteristics and relevant clinical data, such as the onset of symptoms, time of first visit to the neuromuscular clinic, time of establishing the diagnosis, clinical symptoms at diagnosis, and the initial diagnosis, were reviewed and analyzed. All patients were classified according to established clinical phenotypes: ALS classic (spinal onset-cervical and lumbar), ALS bulbar onset, isolated PBP, PLS, and flail-limb (flail-arm and/or flail-leg) PMA based on the observed patterns of disease presentation and progression. The clinical and electrophysiological principles used in the El Escorial/ Awaji criteria.[4,6,25] were adapted to facilitate patient classification.

The frequency of brain and spine magnetic resonance imaging (MRI) studies was recorded. The disease severity was assessed in all cases using the Revised ALS Functional Rating Scale (ALSFRS-R). The outcome measures were determined, which included the following: the time of onset of respiratory failure, the time of starting non-mechanical or mechanical ventilation, and the time of parenteral tube insertion. Follow-up for survival (defined from symptom onset) was conducted at different intervals of clinical visit, and the date of death was also recorded.

Statistical analysis

For descriptive statistics, frequencies of the clinical characteristics were calculated in all participants. Continuous variables were reported as medians, means, and standard deviations (SD). Categorical variables were reported as percentages. All analyses were performed using the Statistical Product and Service Solutions software (SPSS), version 29 by IBM. The starting point for the mean and median survival time was the date of disease onset. The ending point was either the date of death or the first of April 2020 for those who were alive at the study termination.

Results

This study included 29 patients with MND, of which 16 were men and 13 were women, and the male-to-female ratio was 1.23:1. The overall mean age at symptom onset was 54.7±12.7 years, and the oldest patient was an 81-year-old male at the time of symptom onset. The disease duration, from onset to diagnosis, varied among the participants, with a mean period of 20±20.9 months. Most patients presented with significant weakness at diagnosis, with an overall ALSFRS-R of 35.14±10.49. Spinal and brain MRIs were performed (79% and 69%, respectively) to rule out MND mimics. Women had a delay in diagnosis from disease onset (27.5±26.26 months), were more symptomatic than men, and their ALSFRS-R was 30.8±10.31. However, there was no statistically significant difference in the data between men and women (P > 0.05) (Table 1).

Table 1 Demographic and clinical characteristics

Group	Men	Women	ALL	P-value
Participant, N (%)	16 (55.2)	13 (44.8)	29	
Age[1] years±SD	52.06±9.71	56.77±15.63	54.17±12.7	0.299
Duration of disease from onset [1] ±SD, month	14.4	27.5	20±20.9	0.375
Delay in diagnosis from first visit[1]±SD, month	1.6	1.5	1.62 ±1.21 months	0.146
ALS-FRS[1] at diagnosis ± SD	38.6	30.8	35.14±10.49	0.105
Spine MRI	12	11	23(79 %)	0.525
Brain MRI	10	10	20 (69 %)	0.404
Length of follow-up [1]	28	19	24 months	0.600

[1] mean value

Limb weakness was the most common clinical symptom at presentation (82.7%), and bulbar symptoms, such as dysphagia and dysarthria, were present in 62.1% of the patients. Pain was observed in 17.2% at the time of diagnosis, whereas muscle cramps and/or stiffness were present in 13.8% (Table 2). No family history of MND was recorded in any of the patients.

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Table 2 Clinical presenting symptoms

Clinical symptoms	%
Limb weakness	82.7
Dysarthria and/or dysphagia	62.1
Impaired balance	20.7
Muscle wasting	20.7
Pain	17.2
Muscle cramps and/or stiffness	13.8
Depression and anxiety	10.3
Fasciculation	10.3
Weight loss	6.9
Shortness of breath	6.9
Sleep disturbance	6.9

The ALS clinical phenotype (combined bulbar and spinal onsets) was the most common, accounting for 65.6% of the cohort cases. Within the ALS group phenotype, classic ALS was the most frequent phenotype, found in 13 patients (44.8%), whereas the ALS-bulbar onset was seen in 6 patients (20.7%). Isolated PBP and flail-limb PMA subgroups were noted in 4 patients each, representing 13.8%, and only 2 patients belonged to the PLS subgroup (6.9%) (Figure 1).

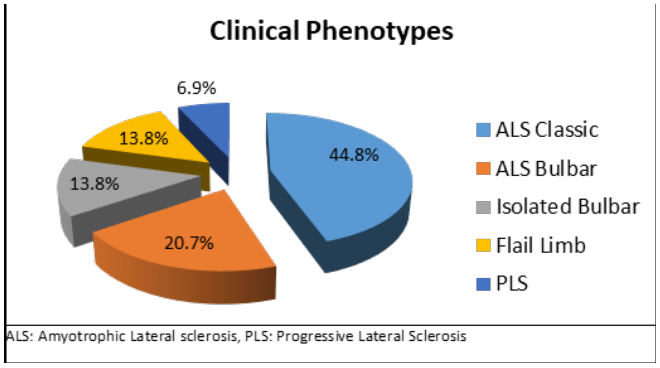

Figure 1 Clinical phenotypes of the patients

Spinal radiculomyelopathy was the most common primary or provisional diagnosis (in 41.3%), brainstem stroke accounted for 20%, and multifocal motor neuropathy with conduction block constituted 14% of the patients. MND was the initial diagnosis in only 6/29 (21%) of the patients (Table 3). Analysis of treatments administered showed that 86% of the patients were on riluzole, 13.8% on edaravone (Radicava), and 10.3% underwent stem cell transplant. By the end of the study, 27.6% of the patients with MND were on mechanical ventilation (invasive and noninvasive) and 34.5% received parenteral tube feeding (Table 4).

Table 3 Initial or primary diagnosis of patients with MND

Initial diagnosis and treatment	Clinical presentation	Number of patients
Cervical radiculopathy	Upper limb weakness	7 (24%)
Lumbosacral radiculopathy	Foot drop/lower limb weakness	3 (10%)
Noncompressive myelopathy	Weakness in both lower limbs	2 (7%)
Local ENT causes	Bulbar muscle weakness	2 (7%)
Multifocal motor neuropathy with conduction block	Weakness in the upper limbs	2 (7%)
Ischemic stroke	Dysarthria and dysphagia	2 (7%)
CIDP chronic inflammatory demyelinating polyradiculoneuropathy	Weakness in both upper and lower limbs	1(3%)
Brachial plexopathy	Unilateral upper limb weakness	1 (3%)
Rotator cuff injury	Unilateral upper limb weakness	1 (3%)
Neuromuscular junction transmission deficit	Respiratory muscle weakness	1 (3%)
Myopathy	Bilateral lower limb weakness	1 (3%)

Note: In 6/29 (21%) cases, MND was considered in the initial differential diagnosis.

Table 4 Drug treatment and supportive measures

	Men	Women	Total, N (%)
Participant, # N	16	13	29
Riluzole	15	10	25 (86)
Edaravone (Radicava)	3	1	4 (13.8)
Stem cell transplant	3	0	3 (10.3)
Mechanical ventilation	3	5	8 (27.6)
Parenteral feeding	4	6	10 (34.5)

By the end of the study, 23 participants (79.3%) survived and 6 (20.7%) died. The median survival time from onset was 4.3 years (51 months) (Table 5). Women had a shorter median survival time than men; However, Kaplan–Meier survival curves revealed no significant survival rate difference (p = 0.61) (Figure 2).

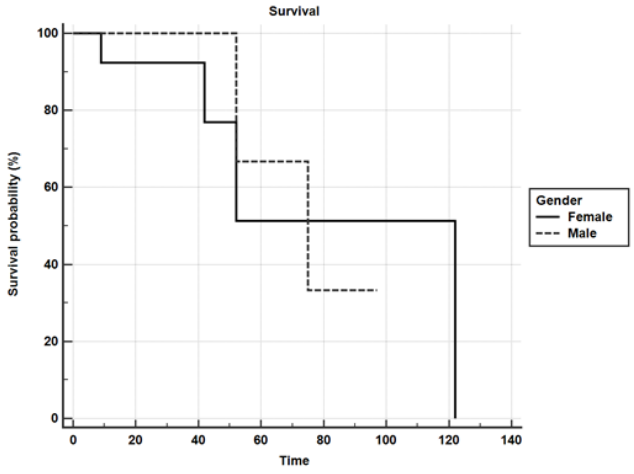

Figure 2 Kaplan–Meier survival curves in men and women

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Table 5 Survival outcome

Group	Men	Women	Total
Number of subjects	16	13	29
Median survival time in months	90	42	51
No. of survival	14	9	23
No. of deaths by the end of the study	2	4	6

Discussion

Most of the currently known clinical characteristics of MND come from studies in Europe and North America. However, recently it has been reported that the epidemiologic characteristics and clinical manifestations of this disease vary depending on the ethnicity of different populations.[20,26,27] Therefore, this study aimed to investigate the characteristics, clinical phenotypes, management strategies, and outcomes of MND in Oman.

Family history of the disease was not observed among the participants, and approximately 90%–95% of ALS/MND has been reported to be sporadic.[28] The male-to-female ratio was 1.23, which is close to the ratio of 1.3–1.56 reported in other studies.[28–32]

In our patients, the age range at disease onset was 24–81 years, with a mean of 54.17±12.7 years, which was lower in men than in women (52.06±9.71 years and 56.77±15 years, respectively). A wide range has been reported for the mean age of patients with MND (46–64 years) as well as for the mean age at onset (58–63 years) for sporadic ALS.[33] A similar finding of a lower age at onset in men than in women has been reported.[34]

Our study found that 69.0% of the patients had limb weakness (spinal onset) as a symptom of onset, whereas 41.4% presented with bulbar symptoms (bulbar onset). Other studies have reported similar findings,[14,35] and some investigations have observed a lower incidence of bulbar symptoms.[31,36] Bulbar symptoms were more common in women than in men (66.3% and 31.3%, respectively) in our study, which is aligned with other reports.[31,35]

Pain was a neglected symptom of ALS until a decade ago.[36] Several studies have focused on pain in ALS and have documented immense variabilities in its frequency among patients, ranging from <15% to up to 85%.[37–41] The pain frequency noted in our study was 17.2%, and it was more common in women (30.8%) than in men (6.3%). The mean duration from onset to diagnosis in this study was 20±20.9 months, and it was longer in women than in men (27.5±26.26 months and 14.4±11.26 months, respectively). Slightly shorter mean durations have been reported in previous studies.[34,42]

ALS has been shown to account for approximately 70% of all cases of MND, the classic limb-onset ALS subtype constitutes approximately two-thirds of all cases of ALS, and the remaining one-third is the bulbar-onset subtype.[43,44] Our study noted comparable findings. Approximately 7% of our patients had the PLS type, which has been shown to be responsible for up to 5% of all cases of MND.[3,7] In contrast, PMA constitutes approximately 10% of the cases.[43,45] This study obtained a slightly higher percentage of PMA in its flail-limb variant (13.8%), which could be attributed to the small cohort included. However, UMN signs can develop late during PMA; in such a case, the diagnosis might be changed to classic ALS.[46] This change may also account for the variable percentages reported, as several patients may start with one phenotype and progress to the complete clinical picture of classic ALS. Similarly, a higher rate of the isolated PBP type was observed in our patients (13.8%), whereas the figures reported in the literature range from 1% to 2%.[3,7] This observation could be attributed to the modest sample size of this study.

Knowledge of the common MND masquerades may aid in the early diagnosis of the disease and in avoiding unnecessary therapies; therefore, the initial diagnosis of our patients was also analyzed as all of them initially attended secondary care hospitals. In 23/29 (79%), a diagnosis other than MND was made, and only in 6/21 (21%), MND was considered as the initial diagnosis.

Cervical radiculopathy was the most common condition considered instead of MND (25%), and one of the patients also underwent surgery. Several patients with MND can have concomitant cervical spondylosis and be often treated as cervical spondylotic radiculopathy, thus delaying the diagnosis. Similar findings have been reported by other studies.[47,48] Approximately 10% of our patients experienced isolated unilateral lower limb weakness presenting as foot drop and were diagnosed as lumbar radiculopathy or plexopathy. Similar cases have been documented earlier, leading to the delayed diagnosis of MND.[49] Furthermore, two of our patients were initially considered to have multifocal motor neuropathy with conduction block and were treated for this condition. This slowly progressive pure motor disease can mimic the upper limb-onset MND. A weakness out of proportion to the wasting with the absence of bulbar involvement may aid in differentiating it from MND.[50]

Rarely, strokes can also mimic MND. The loss of voluntary control of facial and masticatory muscles can occur in the rare Foix–Chavany–Marie syndrome or in bilateral anterior opercular syndrome. This condition has been mistakenly considered a cause for bulbar weakness in a patient with bulbar-onset MND.[51] Two of our patients with MND having bulbar-onset symptoms received an initial diagnosis of local structural pathology. Hence, it is important to note that in MND, the initial symptoms of dysarthria always precede dysphagia. One of our patients with MND presented with respiratory muscle weakness and was initially considered to have myasthenia gravis (MG) and treated for this condition. In patients with bulbar weakness, differentiating between MND and MG is very difficult. Acetylcholine receptor antibodies can be negative in patients with MG, and muscle fatigue that responds to pyridostigmine can occur in both conditions.[52] Moreover, pyridostigmine can cause fasciculations, especially if administered in high doses.[53] One of our patients, who presented with bilateral lower limb weakness, was initially diagnosed as having inflammatory muscle disease. Patients with MND can have elevated creatine phosphokinase levels, and case reports of polymyositis mimicking MND have been published.[54]

Another interesting finding in our study is that bulbar-onset MND was observed in 5 out of 6 cases (83%) in which MND was considered in the initial differentials. The significant early symptoms and rapidity of progression might have aided in considering MND initially in these cases. Three medical treatments have been shown to prolong survival: NIV, gastrostomy feeding, and riluzole.[16,55] The frequency of mechanical ventilation (noninvasive and invasive) among patients in our study was 27.6%, gastrostomy feeding was 34.5%, and riluzole was used in 86% of the cases. Our finding agrees with a longitudinal study of ALS by Demetriou et al. in 2019, which reported that 18% of the patients were on mechanical ventilation, 34% underwent gastrostomy placement (percutaneous endoscopic gastrostomy (PEG) feeding), and 84% received riluzole.[56] Another study has reported that 23.5% of the patients with MND underwent PEG, 10.4% received NIV, and 6.3% had tracheostomy.[35] Riluzole has been reported to be taken regularly throughout the course of the disease by 51.6%–60.9% of the patients.[35,57]

The median survival time from symptom onset was 4.3 years in our study, which is longer than that reported in other studies. Testa et al. documented 2.9 years,[34] while a population-based study conducted in Italy observed a median survival of 2.5 years.[32] In addition, our 4-year survival rate (79.3 %) is higher than that reported by Testa et al. (2004).

The median survival rate in our study was shorter in women than in men, but the difference was not statistically significant in survival

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rate. A similar finding has been reported by Testa et al.[34] The ALS-FRS-R at diagnosis can predict prognosis and survival.[58] The mean ALS-FRS-R at diagnosis in our study was 35.14±10.49, which is close to that reported in other studies.[58,59]

This study is the first in Oman to investigate the clinical characteristics, clinical phenotypes, management strategies, and outcomes of MND. The prevalence and incidence of MND could not be calculated as ours was a hospital-based study. Nonetheless, the findings could be utilized as baseline data for an improved understanding of the characteristics of MND in our country and, consequently, for better management of the disease. Our study is limited by its small sample size as MND is a rare disease in which the patient's survival is short and the diagnosis is delayed. Therefore, a multicenter study involving local and regional centers and longer follow-up (5–10 years) is recommended in the future to increase the sample size and enhance our understanding of the incidence, prevalence, clinical characteristics, and outcomes of MND in this geographic region.

Conclusion

This study is a novel, comprehensive report on Omani patients with MND, which has broadened our understanding of the clinical characteristics of this fatal neurodegenerative disease. This study revealed that the epidemiological and clinical characteristics of patients with MND in Oman are similar to those observed in the international populations but demonstrated a higher survival rate, which can be explained by the early use of supportive interventions. Women faced a longer duration of diagnostic delay and had a shorter median survival time than men. Local and regional multicenter studies are required to augment our comprehension of the incidence and clinical characteristics of MND.

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Conflicts of interest

The author declares no conflicts of interest.

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Ethical approval

The study approval was granted by the Research Ethics Committee, Khoula Hospital-MOH (Code PRO012021073).

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