



Profile of Neuromuscular Disorders: Neurology Clinic, Tripoli Children Hospital

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Abstract

Objective Neuromuscular disorders (NMDs) are any diseases affecting the lower motor neuron (anterior horn cell, peripheral nerve, and neuromuscular junction) or muscle, all of which are components of motor unit. The aim of this study was to describe the clinical, demographic, and genetic profile of children diagnosed with different NMDs.

Materials and Methods Descriptive case series study where clinical records for children with neuromuscular disorders (NMDs) how presented to the outpatient Neurology Clinic at Tripoli Children Hospital in the period from January 2015 to the date of data collection May 2023 have been reviewed to obtain the relevant information which include demographic data, parental consanguinity, family history of affected other members, diagnostic groups within NMDs used were spinal muscular atrophy (SMA) and its subtypes, Duchenne muscular dystrophy (DMD), limb girdle muscular dystrophy (LGMD) and any other NMDs, genetic testing results, ambulatory state at the time of data collection, age at death if occurred, mode of treatment (steroid for patients with diagnosis of DMD, oral Risdiplam/IV Zolgensma/intrathecal Spinraza for patients with SMA) and Genetic testing results and the eligibility to spesfic exon skipping therapy for DMD patients.

Results The study revealed 53 patients with NMDs, which represent 3.8% of all neurological disorders. Of these, 32 (60.4%) were males and 21 (39.6%) were females. Patient ages ranged between 2 months and 20 years (mean = 10 years). SMA and DMD are more common than the other disorders. 77.4% of patients were have positive consanguinity and 66% are have family history. 54.7% of patients still have ability to walk independently. Four (7.5%) patients were died three of them were have diagnosis of SMA type 1 and they died before age of 18 months and the fourth who has diagnosis of SMA type 3 was die at age of 12 years.

Conclusion Although neuromuscular disorders are rare as individual disease entities, as a group they are not. The retrospective study presented here could form the backbone of a future Libyan neuromuscular registry, which is necessary with many novel NMD therapies in pipeline.

Keywords

- ▶ neuromuscular disorders
- ▶ spinal muscular atrophy
- ▶ Duchenne muscular dystrophy
- ▶ limb girdle muscular dystrophy
- ▶ novel NMD therapies

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Introduction

Neuromuscular diseases (NMDs) are any diseases affecting the lower motor neurons (anterior horn cell, peripheral nerve, neuromuscular junction) or muscles, all of which are components of the motor unit. The notion that a pathologic abnormality in a neuromuscular disease may be purely isolated to one anatomic region of the lower motor neuron with primary or secondary changes isolated to muscles is only true for selected conditions. Many neuromuscular diseases are multisystem disorders affecting multiple organs. For example, Duchenne's muscular dystrophy (DMD) gives rise to abnormalities of the skeletal and cardiac muscle, cardiac conduction system, smooth muscle, and brain. This dysfunction can be inherited or acquired.¹ To date, 1,079 NMDs, classified into 16 categories, have been associated with 608 nuclear and mitochondrial genes.² The overlapping and often nonspecific symptoms observed in NMD patients have made the process of differential diagnosis rather complex.² Moreover, the large number of genes and wide range of genetic alterations linked to these diseases have further complicated the diagnosis. Advances in the field of molecular biology and the emergence of high-throughput approaches such as microarray analysis and next-generation sequencing (NGS) have significantly enhanced the identification of novel NMD genes and improved the diagnostic process.³ A systematic approach toward the diagnosis and management of hereditary NMDs is needed, especially in the Middle East where the prevalence of these diseases is thought to be high and underestimated.^{4,5} Lack of NMD-related data in Libya makes it difficult to understand and quantify their socioeconomic impact, concurrent with retrospective studies calling for a much needed infrastructure for data collection and sharing in the Middle East.^{5,6} Establishing a patient registry would address this challenge and enable clinicians, researchers, policy-makers, and industry experts to unify their efforts in introducing new treatment methods and providing better patient care.⁷

The aim of this study was to describe the clinical, demographic, and genetic profile of children diagnosed with different NMDs.

Patients and Methods

Descriptive case series study where clinical records for children with neuromuscular disorders (NMDs) who presented to the outpatient Neurology clinic at Tripoli Children Hospital in the period from January 2015 to the date of data collection May 2023, have been reviewed to obtain the relevant information, which include sex, age, place of residence, consanguinity, family history of affected other members, diagnostic groups within NMDs used were spinal muscular atrophy (SMA) and its subtypes, DMD, limb girdle muscular dystrophy (LGMD) and any other NMDs, genetic testing results, ambulatory state at the time of data collection, age at death if occurred, mode of treatment (steroid for patients with diagnosis of DMD, oral Risdiplam/IV Zolgensma/Intrathecal Spinraza for patients with SMA) and

Genetic testing results and the eligibility to specific exon skipping therapy for DMD patients. The data were coded and analyzed by the SPSS software. Frequency, percentage, mean, and standard deviation were used to describe the data. The chi-squared test was used to find the level of significant difference between categorized data. A *p*-value less than 0.05 was considered significant.

Results

The study revealed 53 patients with NMDs, of which 32 (60.4%) were males and 21 (39.6%) were females. NMDs as a group represent 3.8% of all neurological disorders. Patient ages ranged between 2 months and 20 years (mean = 10 years). In all, 41% of patients were residents of Tripoli, while 13.2 and 11.2% of patients were from Alzawia and Tandamira, respectively. SMA and DMD are more common than the other disorders (► **Table 1**). In total, 77.4% patients were had positive consanguinity, with the highest consanguinity rate (100%) in patients with LGMD. Those with a family history of NMDs accounted for 66% of the patients. All patients underwent confirmatory molecular diagnosis. ► **Table 2** describes the genetic testing results, ambulatory status, and eligibilities to undergo treatment among patients with DMD. Most (75%) patients with DMD were on regular oral prednisolone. More than half (54.7%) of the patients still had the ability to walk independently and 32.1% were bound to a wheelchair. Four (7.5%) patients died, of which three were diagnosed with SMA type 1 and died before the age of 18 months and the fourth who was diagnosed with SMA type 3 died at the age of 12 years. ► **Table 3** describes the correlation between the clinical status and treatment modes of patients with different types of SMA.

Discussion

Neuromuscular disorders (NMDs) represent a large group of conditions that affect the functioning of the muscle, causing progressive weakness. Associated extramuscular involvements constitute chronic comorbidities that disturb the patient's quality of life. There are challenges to better serve patients with chronic NMDs that require a multidisciplinary approach. A systematic approach toward the diagnosis and management of hereditary NMDs is needed, especially in the Middle East, where the prevalence of these diseases is considered high and underestimated.^{4,5} Depending on the exact disease type, incidence rates between 1 and 5 out of 10,000 children have been reported.⁸ However, the most striking finding in this study is that NMDs as a group represent 3.8% of all neurological disorders, which correlate with a Sudanese study where NMDs represented 3.2% of all neurological disorders.⁹ Although muscular diseases are monogenetic disorders inherited in an autosomal recessive (AR), dominant or X-linked pattern, the marked variability in genetics and presentations can be identified within the same category of a subtype and among patients with involvement of the same gene. Arab populations are characterized by a high rate of consanguineous marriages, which favor the

Table 1 Frequency and sex distribution of neuromuscular disorders

NMDs	Patient no. (%)	Gender	
		Male	Female
SMA	28 (52.8%)	11	17
DMD	12 (22.6%)	12	0
LGMD	10 (18.9%)	1	4
CMT	1 (1.9%)	1	0
Nemaline myopathy	1 (1.9%)	1	0
Central core disease	1 (1.9%)	1	0

Abbreviations: CMT, Charcot–Marie tooth; DMD, Duchenne muscular dystrophy; LGMD, limb girdle muscular dystrophy; SMA, spinal muscular atrophy.

Table 2 Frequency of genetic testing and eligible therapy for patients with Duchenne muscular dystrophy (DMD)

	Patient no. (%)	Ambulatory status		Eligible therapy
		Ambulatory	Nonambulatory	
Deletion exon 44	4 (33.3)	2	2	IV Amondys 45
Deletion exon 49–50	1 (8.3)	0	1	IV Exondys 51
Deletion exon 1–52	1 (8.3)	1	0	Not eligible
Deletion exon 8–13	1 (8.3)	0	1	Not eligible
Nonsense mutation	2 (16.7)	1	1	Oral Translarna
Undetermined deletion	3 (25)	2	1	Not eligible

Table 3 Relation of spinal muscular atrophy (SMA) type with other characters

Patient no.		Type 1	Type 2	Type 3	p-value
		7 (25%)	12 (42.8%)	9 (32%)	
Gender	Male	5	2	4	0.052
	Female	2	10	5	
Mode of treatment	Risdiplam	3	11	9	0.063
	Risdiplam + Zolgensma	2	0	0	
	Risdiplam + Spinraza	1	1	0	
	Nil	1	0	0	
Clinical status	Ambulatory	0	5	7	0.001
	Nonambulatory	1	7	1	
	<6 mo old	3	0	0	
	Death	3	0	1	

appearance of such groups of muscular and neuromuscular diseases in multiple and successive generations.¹⁰ In the present study, 77.4% of patients had parental consanguinity. It is generally believed that consanguinity has no significant effect on the occurrence of autosomal dominant or X-linked diseases. This fact corroborates with our findings in which only 41% of patients with DMD had parental consanguinity as compared with 100 and 85.7% for patients with LGMD and SMA, respectively. Also, these findings are consistent with data obtained in Ben Halim N et al where parental consanguinity was associated with an eightfold to ninefold in-

creased risk of recessive disease expression.¹¹ Clinically focused community surveys and hospital studies have offered brief insight into the spectrum of NMDs in the Middle East, including studies in Egypt with sparse reporting on a multitude of NMD subtypes.¹² The present study found SMA to be the most frequently occurring NMD (52.8%), followed by DMD and LGMD with frequencies of 22.6 and 18.9%, respectively. This is contrary to the reports that have revealed the prevalence and profiles of NMDs in the region. In a 43-year study with 823 NMD patients from Cairo, DMD and autosomal MDs were reported as the most common

NMD, followed by lower rates of SMA and congenital myopathies. Charcot-Marie tooth (CMT) disorders were less frequent, along with myotonic dystrophy identified in a relatively fewer patients.¹³ SMAs are characterized by premature degeneration of the second motor neuron. 5q-associated SMA is by far the most common form with an incidence of about 1 in 6,000 to 10,000 live births. The phenotype is broad and ranges from infants dying within the first year of life due to respiratory insufficiency to patients showing first symptoms of mild proximal muscle weakness beyond the age of 18 years. The disease is caused by biallelic mutations in the Survival Motor Neuron (SMN1) gene. About 95% of patients carry homozygous SMN1 deletions of exon 7 or exons 7 and 8, resulting in a truncated and unstable SMN protein. While biallelic mutations in SMN1 cause SMA, disease severity is related to the number of SMN2 copies.^{14,15} In our study, 25% of patients had homozygous deletion of exon 7 with two copies of SMN2 protein and 42.9 and 32% of these had a homozygous SMN1 deletion of exons 7 and 8 with three and four copies of SMN2, respectively. The Food and Drug Administration (FDA) in 2017 and the European Medical Agency (EMA) in 2018 approved Nusinersen (Spinraza R), an antisense oligonucleotide that modifies the splicing process of SMN2, thereby enhancing the production of stable and functional SMN protein. Onasemnogene abeparvovec (Zolgensma) is an Adeno Associated Virus 9 (AAV9) vector-based gene therapy approved in 2019 by the FDA for children with SMA under the age of 2 years and Risdiplam (Evrysdi) is a small molecule modifying pre-mRNA splicing of SMN2. The drug is studied in patients with SMA 1 to SMA 3 and in presymptomatic SMA 1 patients. Risdiplam can be given orally since it penetrates the blood-brain barrier. Currently, many SMA 1 patients start treatment with one of the above-mentioned therapeutic agents after they have been diagnosed. Although the efficacy of these new drugs has been well documented in clinical trials, improvement of motor function is often modest, and swallowing and respiration remain substantially compromised.^{16,17} This stands in sharp contrast to the results of studies with nusinersen and onasemnogene abeparvovec in presymptomatic SMA 1 patients, showing that many of them were able to walk, learn to speak, and remain ventilator free at least within the first years of life.^{18,19} These data strongly support the inclusion of SMA in newborn screening programs.^{20,21} A clinically relevant finding in this study is that the mortality rate was higher in SMA 1 patients than in other NMDs. The other groups of SMA have a similar curve to the DMD patients, but the decline starts earlier, just before 10 years of age, and these findings are consistent with the literature.²² DMD is caused by mutations in the dystrophin gene, located on Xp21. The dystrophin gene is one of the largest human genes and has 79 exons. Our study revealed that 50% of DMD patients lost their ability to walk at the time of data collection. This is consistent with the finding in other studies that show that most patients become wheelchair bound until the age 12 years. Scoliosis, cardiomyopathy, and respiratory failure evolve thereafter and result in premature death

without assisted ventilation by the age of 20 years.²³ Recommended standards of care have been published,^{24,25} and their transformation into clinical practice (e.g., steroid treatment, spinal surgery, noninvasive ventilation) has delayed the age at loss of ambulation and substantially increased the life expectancy.^{23,26,27} Large deletions disrupting the reading frame account for 65% of mutations, and approximately 10% of patients carry nonsense mutations resulting in premature termination of the protein synthesis.²⁶ In the current study, 16.7% of DMD patients carry nonsense mutation. Steroids were the first drugs to improve muscle strength and pulmonary function.^{25,28} It is supposed that prednisone reduces the inflammatory process as a result of the cell membrane breakage. Ataluren (Translarna) is approved by the EMA, but not yet by the FDA, for treatment of ambulant DMD patients older than 2 years with nonsense mutations in the dystrophin gene.²⁹ Exon skipping therapies aim to restore the reading frame in DMD patients with deletions. This allows production of a shortened and defective, but still functional, dystrophin protein.³⁰ Among boys with deletions, approximately 20% patients are amenable to skipping of exon 51, 13% to skipping of exon 53, 12% to skipping of exon 45, and 11% to skipping of exon 44. Eteplirsen (Exondys 51) received an accelerated approval by the FDA in 2016 for the treatment of DMD patients with mutations amenable to skipping of exon 51.³⁰ Several new therapeutic options have become available for the treatment of pediatric NMDs in the last years, and multiple others are currently under preclinical and clinical trials. While some diseases have now become principally treatable, many others are still waiting for a major breakthrough.

Conclusion

The summed estimate for NMDs as a group represents only the tip of the iceberg. Although neuromuscular disorders are rare as individual disease entities, as a group, these are not uncommon. The retrospective study presented here could form the backbone of a future Libyan neuromuscular registry, which is necessary with many novel NMD therapies in pipeline.

Authors' Contribution

All the named authors contributed to the clinical care of the patients, data collection, drafting and revising of the manuscript, and approval of the final version of the article.

Compliance with Ethical Principles

This is a small case series that does not require prior ethical approval. All patients and/or their patients/guardian signed a general consent form allowing anonymous use of data for education, research, and quality improvement.

Funding and Sponsorship

None.

Conflict of Interest

None declared.

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