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Muscle dystrophies in children: Genetic and clinical correlation

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Abstract---Muscular dystrophies are a heterogeneous inherited group of disorders characterized by a variable distribution of weakness, various ages of onset, the pattern of inheritance, rate of progression, and clinical severity. Muscle degeneration and regeneration characterize muscle biopsy and these disorders are typically associated with elevated serum creatine kinase. Objective: We wanted to study the clinical characteristics of patients with muscle dystrophies and study clinical and genetic correlation in patients with Duchenne muscular dystrophy. Methods: This cross-sectional descriptive study included a cohort of 60 patients diagnosed with muscular dystrophy and fulfilling the inclusion criteria. All patients were subjected to full history taking and full neurological examination. Results: Patients are divided into five groups to study clinical characteristics in each group. 1. Duchenne muscular dystrophy group: included 30 patients who have genetically confirmed DMD cases (50 %), 2. Limb-girdle muscular dystrophy group: included 23 patients (38.3 %), 3. Myotonic dystrophy group: included 3 patients (5 %), 4. Congenital muscular dystrophy group: included 3 patients who were diagnosed clinically as merosin deficient congenital muscle dystrophy (5 %), 5. Distal dystrophy group: included 1 patient with distal muscle dystrophy (1.7 %). Mean age, gender, age of symptoms onset, main motor symptoms, CPK level, echocardiography. Conclusion: Muscular dystrophies are a heterogeneous inherited

group of disorders. Genetic analysis is important for confirming the diagnosis of muscular dystrophies and assessing the amenability of newly emerging therapies.

Keywords---muscle dystrophies, DMD, LGMD, DM, distal dystrophy, genetics.

Introduction

Muscular dystrophies are a group of more than 30 genetic inherited diseases that cause increasing degeneration of skeletal muscles and progressive muscle weakness [1]. Over time many patients lose the ability to walk and will often die prematurely. Muscular dystrophies are clinically divided by age of onset, rate of progression, severity of symptoms, distribution of muscle weakness, and pattern of inheritance [1]. In 1986, the first causative gene was identified for the most prevalent and best-characterized form of muscular dystrophy, namely, Duchenne muscular dystrophy [2].

Currently, the diagnosis is generally made on clinical grounds and confirmed by genetic testing, serologic assessments, neurophysiologic measurements, or muscle biopsy [3]. Dystrophic changes in affected muscles usually do not occur randomly but rather develop in a specific pattern [4]. Detecting a specific pattern of muscular involvement is therefore often used to narrow down the genes to be sequenced and evaluated [4]. Muscle biopsies suffer from sampling errors and are invasive procedures. Thus, their use may be limited in the assessment of disease status in muscle dystrophies (MDs), especially because young children are commonly affected and repeated evaluations are necessary due to the tendency of muscles to degenerate over time. An imaging approach is desired in this case [3].

Numerous imaging methods exist to evaluate skeletal muscles in the various MDs and to track disease progression including computed tomography (CT), nuclear medicine (e.g., positron emission tomography, PET and single-photon emission computer tomography, SPECT), ultrasound (US), and magnetic resonance imaging (MRI)[3]. In pediatric populations, the use of nuclear medicine and CT have the disadvantage of exposing patients to ionizing radiation, even though the sensitivity and specificity are notably high (especially for PET)[3]. Advances in the MRI acquisition particularly at higher magnetic field strengths have led to the introduction of whole-body MRI protocols that allows evaluation of the entire muscles leading to a complete involvement pattern including clinically relevant anatomic regions such as the shoulder girdle, upper extremities, and the head and neck region[3]. In addition, whole-body MRI protocols allow the evaluation of organ systems beyond the skeletal muscle including the lungs, heart, and abdominal organs [4].

Treatment for nearly all forms remains supportive and aims to prevent complications[2]. However, several promising approaches have entered clinical trials, providing tangible hope that quality of life will improve for many patients shortly [2]. This study aims to assess the clinical characteristics of patients with muscular dystrophies. This will allow physicians to give patients a better idea of

prognosis and to offer useful interventions, such as cardiorespiratory surveillance, for at-risk groups.

Patients and Methods

This observational analytical study was carried out at the Pediatric Neurology Unit, Cairo University Children's Hospital during the period between October 2019 and June 2021. The study included 60 patients diagnosed with muscular dystrophy and fulfilling the inclusion criteria.

Inclusion criteria: 1. Patients diagnosed with Duchenne muscular dystrophy by genetic analysis and who are following in Neuromuscular Clinic during the period of study. 2. Patients with progressive muscle weakness with high serum level of creatine kinase (CK) and with electromyogram (EMG) suggestive of myopathy who are not diagnosed with Duchenne muscular dystrophy.

Exclusion criteria: 1. Patients with other causes of muscle weakness as congenital myopathies, myasthenia gravis, or disorders of peripheral nerve.

Methodology

All patients in the study were subjected to meticulous clinical history including:

1. Age, gender, duration, and course of illness
2. Family pedigree included: Consanguinity, gender of siblings, the total number of siblings, similar conditions among siblings, and their order.
3. History suggestive of perinatal insult: Decreased fetal movements, obstructed labor, postnatal cyanosis, and history of NICU admission.
4. Present history: Motor delay, the onset of muscle weakness, fatigue, muscle cramps, difficulty walking, difficulty climbing stairs, gait abnormalities, and recurrent falls.
5. Complications:
 - Skeleton and muscle: Contractures, pseudohypertrophy, lordosis, scoliosis, and age of onset of immobility.
 - Cardiorespiratory: Cardiomyopathy, breathing difficulties, respiratory infections, and sleep apnea.
 - Nervous system: Developmental delay, motor delay, and learning disability.
 - Gastrointestinal: Dysphagia, constipation, reflux and gastroparesis.

The full detailed examination included: General examination, cardiac examination, chest examination, and neurological examination including Mentality, gait, Gower's sign, tone, reflexes, and power grading according to the Medical Research Council (MRC).

Results

Patients are divided into five groups to study the clinical characteristics in each group: 1. Duchenne muscular dystrophy (DMD) group: included 30 patients who have genetically confirmed DMD cases (50 %), 2. Limb-girdle muscular dystrophy (LGMD) group: included 23 patients (38.3 %), 3. Myotonic dystrophy (DM) group:

included 3 patients (5 %), 4. Congenital muscular dystrophy (CMD) group: included 3 patients who were diagnosed clinically as merosin deficient congenital muscle dystrophy (5 %), 5. Distal dystrophy group: included 1 patient with distal muscle dystrophy (1.7 %).

Table (1): Patients' demographic characteristics in different diagnoses

	DMD	LGMD	DM	CMD	Distal dystrophy	
Number of patients	30	23	3	3	1	
Mean age (years)	9	10.7	7.3	4.7	12	
SD (years)	2.36	3.45	2.3	0.58	-	
Gender	Male	30 (100 %)	9 (39.1 %)	2 (66.1 %)	2 (66.7 %)	1 (100 %)
	Female	None	14 (60.9 %)	1 (33.3 %)	1 (33.3 %)	None
Consanguineous Parents	8 (26.7 %)	14 (60.9 %)	1 (33.3 %)	2 (66.7 %)	None	
Positive family History	8 (26.7 %)	13 (56.5 %)	None	1 (33.3%)	None	

Table (2): Prominent clinical features in the study population

Variables	DMD	LGMD	DM	CMD	Distal
Gait abnormalities	29 (96.7%)	18 (78.3%)	None	3 (100%)	1 (100%)
Muscle cramps	3 (10%)	11 (47.8 %)	2 (66.6%)	none	1 (100%)
Difficulty in climbing stairs	30 (100%)	19 (87.6)	2 (66.6%)	3 (100%)	1 (100%)
Recurrent falls	30 (100 %)	18 (78.3 %)	None	1 (33.3%)	1 (100%)
Motor delay	13 (43.3 %)	8 (34.8 %)	None	3 (100%)	None
Mental delay	6 (20 %)	1 (4.3 %)	None	3 (100%)	None
Learning disability	10(33.3 %)	3 (13 %)	None	3 (100%)	None
Wheel-chair dependency	8 (26.7 %)	2 (8.7 %)	None	None	None
Muscle wasting	2 (6.7%)	1 (4.3%)	1 (33.3%)	3 (100%)	None
Ankle contractures	10 (33.3 %)	2 (8.7 %)	None	None	None
Knee contractures	6 (20 %)	3 (13 %)	None	None	None
Lordosis	20 (66.7 %)	1 (4.3 %)	None	None	None
Scoliosis	4 (13.3 %)	None	None	None	None
Pseudohypertrophy	29 (96.7 %)	9 (39.1 %)	None	None	None
Winging of scapula	None	7 (39.4 %)	None	None	None
Cardiac complications	4 (13.3 %)	4 (12.5%)	1 (33.3%)	2 (66.6%)	None
Respiratory complications	5 (16.7%)	None	1 (33.3%)	None	None

CPK levels varied greatly between different types of muscle dystrophies as shown in the following table:

Table (10): CPK levels varied greatly between different types of muscular dystrophies

	DMD	LGMD	DM	CMD	Distal dystrophy
Mean (IU/L)	12747.8	10390.1	917.33	232103	7315
SD	9802.1	9444.3	858.88	1190.2	-
Minimum	1480	255	310	947	-
Maximum	39818	31219	1900	3017	-

EMG showed myopathic changes in all patients with DMD, LGMD, CMD, and distal dystrophy; while characteristic myotonic discharges were found in all patients with DM.

Echocardiography

In the DMD group: 26 patients had normal Echo (86.7 %). Two patients (6.7 %) had dilated cardiomyopathy and 2 patients had MVP (6.7 %).

In the LGMD group: 19 patients had normal Echo (82.6 %). Two patients (8.7 %) had dilated cardiomyopathy and 2 patients had MVP (8.7 %).

In DM group: 2 patients had normal Echo (66.7 %). one patient (33.3 %) had MVP (8.7 %).

In the CMD group: 2 patients (66.6 %) had normal Echo and one patient (33.3 %) had a bicuspid aortic valve.

MLPA

All 30 DMD patients in our cohort were genetically confirmed to have DMD by MLPA (Multiplex ligation-dependent probe amplification) technique or dystrophin gene analysis in MLPA-negative patients. MLPA was positive in 27 patients (90 %) with DMD showing deletion and duplication mutations. Deletion mutations were found in 23 patients (76 %); while duplication mutation was found in 4 patients (13.4 %). Single exon deletion was found in 6 patients (20 %). Short deletions (more than 1 and less than 5 exons) were found in 3 patients (10 %), while long deletions (≥ 5 exons) were found in 14 patients (46.7 %). The most common deletion mutation was 45-50 in 3 patients (10 %) and 4-43 in 3 patients (10 %). Exon number 45 showed highest deletion rate (6 patients = 26.1 %). Followed by exon number 51 in 4 patients (21.74 %).

Dystrophin gene analysis

Dystrophin gene analysis was positive in 3 patients (10 %) with DMD and revealed nonsense mutations (premature stop codon) and negative in 23 patients with LGMD (100 %).

Discussion

Duchenne muscle dystrophy

Patient characteristics

This group included 30 patients (50 % of the total) with an age range of 4 - 14 years (mean age 9 ± 2.36 years). This was similar to results obtained by *Johnston et al. (2015)*, where the mean age was 9.9 ± 2.6 years. Age distribution in our study was a little different from a previous study by *Polavarapu et al. (2016)*, in which the mean age of DMD patients was 7.6 ± 2.8 years, and another study done by *Salari et al. (2017)*, where the mean age of the study group was 7.29 ± 3.24 years, with an age range similar to our study (3-14) years[7][6].

Clinical and functional aspects

In our study; 8 patients (26.7 %) were the offspring of consanguineous parents. While *Salari et al. (2017)* described positive consanguinity in 35.7% of cases[6]. Positive family history in our study group was present in 8 patients out of 30 (26.6%). Four of them are offspring of consanguineous parents. This is similar to the study done by *Salari et al. (2017)*, where 25 % of cases had a positive family history of DMD[6]. Also, our results were close to results obtained by *Polavarapu et al. (2016)*, in which positive family history was present in 16 patients (32%)[7]. In the current study, the mean age at onset of weakness was 4 ± 1.8 years. Consistent with our findings, *Salari et al. (2017)* reported that all reported cases had shown the onset of symptoms and muscle weakness between 4-6 years of age[6]. Another similar result was described by *Polavarapu et al. (2016)*, where the mean age of symptoms onset was 3.9 ± 2.2 years [7].

According to our study, delay in achieving motor milestones was present in 13 patients (56.7%) and recurrent falls and difficulty in climbing stairs occurred in all patients. Similar results were obtained by *Desguerre et al. (2009)* where 56% of patients had delayed walking, 56% had never been able to run, and 31% had difficulty climbing stairs without support [8]. Also, these results were close to results obtained by *Polavarapu et al. (2016)*, where delayed acquisition of motor milestones was reported in 29 patients (58%)[7]. Eight patients became non-ambulant (26.7 %) with a mean age of onset of wheelchair dependency (8.63 ± 2.13 years). This age was higher than the results described by *Yin et al. (2019)*, where non-ambulant patients were 4/32 (12.5 %)[9]. Also, our results showed an earlier age of non-ambulation compared to results obtained by *Choi et al. (2019)* where the age of ambulation loss was 13.1 ± 2.6 years[10]. Our study results showed that 6 patients with DMD (20 %) had delayed mental development. Learning disabilities were found in 10 patients with DMD (33.3%). This is higher than the results obtained by *Polavarapu et al. (2016)*, who reported that delay in attaining mental milestones was found in 4 patients (8%)[7]. Ankle contractures occurred in 10 patients (33.3%) while knee contractures were found in 6 patients (20 %). That differs from results conducted by *Polavarapu et al. (2016)*, where contractures of the Tendon Achilles were present in 42 (84%) although a similar percentage of knee contractures in 9 (18%)[7]. The mean CPK level in the current study was 12747.8 ± 9802.1 IU/L. Similar results were obtained by *Polavarapu et al. (2016)*, where the mean serum CK level was $14,100.4 \pm 9800.8$ IU/L[7]. In the

present study, scoliosis was found in 4 patients (13.3 %). This number was much lower than the results obtained by *Choi et al. (2019)* were 31/50 (62 %) boys developed scoliosis[10]. This can be explained by the fact that this study enrolled patients who already lost ambulation and followed them up for 2 years. In the current study; 26 patients had normal Echo (86.7 %). Two patients (6.7 %) had dilated cardiomyopathy and 2 patients had MVP (6.7 %). This can be explained as most of the patients included in our study were young (median age of 9 years). These results were similar to results obtained by *Yamamoto et al. (2018)* who stated that up to the age of 7 years, no patients showed cardiac dysfunction while at the age of 14 years, cardiac dysfunction was observed in nearly half of the patients[11]. Similarly, *Pandya et al. (2018)* described that (69.7%) of individuals developed cardiomyopathy at age of 14.9 years[12]. Another explanation is due to delayed recognition may be by relative physical inactivity obscuring symptomatology.

Genetic factors

All 30 DMD patients in our cohort were genetically confirmed to have DMD by MLPA technique or dystrophin gene analysis in MLPA-negative patients. MLPA was positive in 27 patients (90 %) with DMD showing deletion and duplication mutations. Deletion mutations were more common than duplication mutations. Deletions were found in 23 patients (76 %); while duplication mutation was found in 4 patients (13.4 %). Dystrophin gene analysis was positive in 3 patients (10 %) with DMD and revealed nonsense mutations (premature stop codon). This was close to results obtained from a Chinese study by *Chen et al. (2014)* that analyzed 119 unrelated DMD Chinese patients using MLPA and found among them 81 patients (68.1%) with gross deletions/duplications, of which 64 (79.0%) were deletions, 16 (19.8%) were duplications, and one (1.2%) was both deletion and duplication. Eleven patients had small (≤ 3 bps) mutations (9.2%)[10]. A similar observation was reported by *Polavarapu et al. (2016)*, who reported a much more common deletion mutation in (94%) of patients while only (6%) showed duplication mutations[14]. In the current study; single exon deletion was found in 6 patients (20 %). Short deletions (more than 1 and less than 5 exons) were found in 3 patients (10 %), while long deletions (≥ 5 exons) were the most encountered mutation in 14 patients (46.7 %). *Polavarapu et al. (2016)* reported that single exon deletion was found in 27.7% of cases, while less than 5 exons deletion were found in 19.1 % and more than 5 exons were 53.2% which is close to our results[14]. In the present study; exon number 45 showed the highest deletion rate (6 patients = 26.1 5%) followed by exon number 51 in 4 patients (21.74 %) which is different from results obtained by *Polavarapu et al. (2016)* where exon number 51 showed highest deletion rate of 46%[14].

LGMD

Patient characteristics

This group included 23 patients (38.3 % of the total), and six of them were genetically confirmed to have autosomal recessive limb-girdle muscle dystrophy. The remaining patients are suspected to have limb-girdle muscle dystrophy most probably sarcoglycanopathies as they had DMD phenotype and diagnosis of DMD

was excluded in all of them with negative MLPA and dystrophin gene analysis. The patient's age range was from 5 - 16 years with a mean age of 10.7 ± 3.54 years and the median age of 11 years. The mean age at onset of weakness was 5.2 ± 2.7 years and the median age of onset was 4.5 years. Similar results were obtained from a Chinese study of a cohort of 25 patients with sacroglycanopathies by *Wang et al. (2018)* who stated that the median patient age was 10.1 (3.2–27.4) years and the median age at onset was 4.5 (0.8–11)[15]. In the current study, the female gender was more common in patients with LGMD (14 females 60.9% versus 9 males 39.1%). Same results were conducted by *Winckler et al. (2019)*, where the distribution of gender between different subtypes of LGMD showed a predominance of female gender in sacroglycanopathies (68.6 %), LGMD2A (58.9 %) while male gender was more common in LGMD2I (74.1 %) and LGMD2L (83.3 %)[16]. In the present study; 14 patients (60.9 %) were the offspring of consanguineous parents, while 9 patients (39.1 %) were born to non-consanguineous parents. Positive family history was present in 13 out of 23 patients (56.5%); 8 of them are offspring of consanguineous parents. Similar results were obtained by *Winckler et al. (2019)* where consanguinity was reported by (40.2%) of families and (66.7%) were simple cases[16]. In the present study, 17 patients (73.9%) complained of proximal muscle weakness and difficulty in climbing stairs occurred in 19 patients (82.6 %). Abnormal gait was found in 18 patients (78.3%). Recurrent falls were found in 18 patients (78.3%) and muscle cramps occurred in 11 patients (47.8%). The motor delay occurred in 8 patients (34.8%). Two patients (8 %) were diagnosed to have autosomal recessive LGMD after an incidental finding of hyperCKemia. 1 patient (4.3%) complained of winging of the scapula and 1 patient (4.3%) was referred to a cardiomyopathy clinic with dilated cardiomyopathy. Similar results were obtained by *Wang et al. (2018)* where 16 patients (66.7%) had proximal lower limb weakness and frequent falls, gait abnormalities, delayed motor milestones, exercise intolerance, difficulty in running, climbing, and jumping and muscle pain was reported by 29.2% of patients without muscle weakness[15]. Two patients (8.3%) were diagnosed to have sacroglycanopathy after an incidental finding of hyperCKemia. In the current study, two patients became non-ambulant (8.7 %) with a mean age of onset of wheelchair dependency (12.5 ± 0.71 years). According to results obtained by *Wang et al. (2018)*, there were 4 (16 %) patients who were no longer able to ambulate independently at a median age of 18.2 (range 12–26.4) years [15]. In the present study, pseudohypertrophy was found in 9 patients with LGMD (39.1 %). Winging of the scapula was present in 7 patients with LGMD (30.4 %) and muscle cramps occurred in 11 patients (47.8%). Tendon contractures were present in 21.7 % of patients. Knee contractures occurred in 3 patients (13 %) followed by ankle contractures in 2 patients (8.7 %). Different results were obtained by *Wang et al. (2018)* where motor signs included calf hypertrophy in 54.2% of patients, scapular winging in 12.5%, and tendon contractures (in 33.3%)[15]. Another observation that was reported by *Fischer et al. (2005)* which can differentiate LGMD2A and LGMD2I is the rare occurrence of calf pseudohypertrophy (seen in two-thirds of LGMD2I patients) and the absence of cardiac involvement (occurring in about 30% of LGMD2I patients)[17]. In the current study CPK range in the LGMD group was (255–31219 IU/ L) with a mean of 10390.1 ± 9444.3 IU/ L. Similar results were obtained by *Wang et al. (2018)* where CK levels were elevated in all patients (345–35,120 IU/ L)[15]. According to *Winckler et al. (2019)*, CPK levels varied in different subtypes of LGMD and ranged from (46–27 300) in

sarcoglycanopathies, and (141-25 541) in LGMD2A and (46-27 300) in LGMD2I[16]. In the present study; 19 patients had normal Echo (82.6 %). Two patients (8.7 %) had dilated cardiomyopathy and 2 patients had MVP (8.7 %). Studies regarding cardiac involvement in autosomal recessive LGMD report variable degrees of cardiac involvement in different subtypes with the most common subtypes with cardiac involvement being sarcoglycanopathies and LGMD2I. According to *Winckler et al. (2019)*, structural heart abnormalities were present in 40 % of LGMD2I, 5.8 % of sarcoglycanopathies, and 1.2 % of LGMD2B and absent in other subtypes[16].

Myotonic dystrophy

This group included 3 patients (5% of total) with an age range of 6 - 10 years (mean age 7.33 ± 2.3 years). The mean age of onset was 4.33 ± 1.53 years. Regarding gender in this group; there were 2 males (66.1%) and 1 female (33.3%). According to results obtained from a study including 17 patients with DM1 by *Kim et al. (2019)*, the age of onset was in the neonatal period in 58.8 % of patients while 41.2 % of patients presented after the neonatal period up to 15 years[18]. According to *Kim et al. (2019)*, similar to our results, gender distribution was found to be 12 males (70.6 %) and 5 females (29.4 %)[18]. In contrast to that, according to a study done by *Solbakken et al. (2019)*, there were no significant differences in age or gender between the patients and the control group[19]. One patient (33.3 %) was born to consanguineous parents with no positive family history of muscular dystrophy in first-degree relatives. Results obtained by *Kim et al. (2019)* showed that 10 (58.8 %) patients had a positive family history of DM1[18]. The main complaint in the DM group was muscle spasm (myotonia) in all patients. According to *Kim et al. (2019)*, the first symptoms included hypotonia, myotonia, weakness, delayed development, and gait disturbance[18]. In the present study, 2 patients had normal Echo (66.7 %) and one patient (33.3 %) had MVP (8.7 %). Results obtained by *Kim et al. (2019)*, showed the presence of arrhythmia in only 1 patient (5.8 %)[18]. According to our results, 1 patient (33.3 %) had learning disabilities. Literature reviews reported minor intellectual deficits in many patients with childhood-onset DM1 [20].

Congenital muscle dystrophy

In our study, this group included 3 patients (5% of total) who were suspected to have CMD (clinical presentation and magnetic resonance imaging compatible with merosin deficient congenital muscle dystrophy) with an age range of 4 - 5 years (mean age 4.67 ± 0.58). The disease onset was dating since birth. Regarding gender in this group; there were 2 males (66.1%) and 1 female (33.3%). Two patients (66.7 %) were born to consanguineous parents with a positive family history of muscular dystrophy in one patient. According to a study including 26 patients with clinical presentation, magnetic resonance imaging, and/or laminin- $\alpha 2$ expression in muscle compatible with MDC1A done by *Oliveira et al. (2008)*, the age ranged from 3 months to 27 years [21]. The age of onset in utero was found in 3 patients (11.5 %) and the onset of symptoms since birth was found in 19 patients (73 %). The maximum age of onset of symptoms was 3 years. *Oliveira et al. (2008)* reported also that none of the families were consanguineous [21]. In the present study, a floppy infant with generalized hypotonia was the main

presentation in all patients. Muscle wasting was found in all the patients with CMD (100 %). All patients showed delays in the achievement of motor milestones. Similar to our results, *Oliveira et al. (2008)* reported that all patients presented with hypotonia with or without contractures except one patient with a peculiar presentation with progressive spastic paraparesis followed later by a slowly progressive neuropathy [21].

Distal muscle dystrophy

In the present study, 1 of our patients was a male aged 12 years. He was born to nonconsanguineous parents. He presented with distal muscle dystrophy at the age of 2 years with no family history of other family members' affection. There is a history of polyhydramnios. He had normal development but walked with difficulty and there was a history of muscle cramps, recurrent falls, and difficulty in ascending stairs. He presented with muscle weakness which is more distal than proximal.

According to literature, distal myopathies are a diagnostically challenging group of diseases. A study was done by Bugiardini et al. (2018) on 55 patients with distal weakness or who had predominantly distal weakness at assessment and underlying pathogenesis was considered myopathic based on the overall analysis of neurophysiological (electromyography, EMG) or muscle biopsy[22]. The cohort included 10 patients with childhood disease onset (<10 years old), 22 patients with juvenile/adult-onset (10–39 years), and 23 patients with late-onset (>40 years old) disease. The initial genetic diagnostic rate was 39%; 18% were misdiagnosed as neuropathies and 13% as inclusion body myositis (IBM) [22].

Correlations

Genetic analysis results (single exon deletion, less than 5 exons deletion, ≥ 5 exons deletion, duplication mutation, and nonsense mutation) showed no correlation with either age of disease onset, or onset of wheelchair dependency. Studies are limited in this aspect; however, our findings were consistent with the observations made in a study done by *Polavarapu et al. (2016)* who stated that there was no correlation between the location of deletion/duplication with muscle MRI findings Mercuri score[14]. Further, the number of exons deleted did not correlate with muscle MRI scoring[14].

Conclusion

Muscular dystrophies are a heterogeneous inherited group of disorders that can be distinguished by variable distribution of weakness, various ages of onset, the pattern of inheritance, rate of progression, and clinical severity. Genetic analysis is important for confirming the diagnosis of muscular dystrophies and assessing the amenability of newly emerging therapies. When routine MLPA testing is negative, muscle MRI findings along with clinical phenotype could help in proceeding to the next level of genetic testing. There is no correlation between different gene mutations in DMD and age of onset of symptoms, age of loss of ambulation, or disease severity.

Recommendation

Sequential studies to follow the progression of muscle involvement in progressive disorders. This would allow us to obtain information not only about the state and progression of the pathology of individual muscles but also more generally about the natural history of the conditions studied. These data can provide an important baseline for ongoing therapeutic studies, such as those using antisense oligonucleotides in patients with DMD. The opportunity to assess the progression of pathological changes in individual muscles in treated and untreated patients may provide valuable information on the efficacy of the treatment and may represent an alternative to serial muscle biopsies.

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