

How to Cite:

Balamurugan, N., Muthukumaran, D., Sangeetha, S., & Balasubramanian, S. (2022). Hospital based study on demographic profile and clinical spectrum on hereditary muscle disorder. *International Journal of Health Sciences*, 6(S1), 13813–13825. <https://doi.org/10.53730/ijhs.v6nS1.8499>

Hospital based study on demographic profile and clinical spectrum on hereditary muscle disorder

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Abstract--Background: Myopathies are disorders in which a primary functional or structural impairment of skeletal muscle. In general, Muscle disorders are classified into hereditary and acquired disorders. The approach to a patient with a suspected muscle disease is to determine the correct site of the lesion from history and physical examination. This will help to decide on management and prognostication issues. We undertook this study of hereditary muscle disorders to identify the demographic profile and clinical spectrum of hereditary muscle disorders. Aims and Objectives: To study the demographic profile of patients with hereditary muscle disorders and to study the clinical spectrum of hereditary muscle disorders. Methods and Materials: A cross sectional study was conducted on Institute of Neurology, Madras Medical College, Chennai during the period of July 2018 to February 2019 (8 months), among 44 patients (Males-32, Females-12), with clinical features suggestive of hereditary muscle disorders, with certain exclusion criteria's. Clinical evaluation was done by detailed history taking followed by general and CNS examination, along with motor system examination. All the data were tabulated in Microsoft XL sheet, followed by analysis using SPSS software (version 20.0). Results: In our study with a total of 44

patients, 32 (72.7%) were males and 12 (26.3%) were females. In LGMD out of 25 patients, 16 (64%) were males and 9 (36%) were females, in a total of 44 patients with hereditary muscle disorders, 40 (91%) were muscular dystrophies. LGMD is the most common hereditary muscle disorders in our study (57%) The age distribution in our patients showed that 20% of the patients were in the age group of less than 15 years All 2 (100%) patients with congenital myopathy had age at onset in 3rddecade.This shows that our patients with congenital myopathy could be the milder adult onset variants. Among 44 patients only 4 (9.1%) patients had asymmetric weakness. Most of our patients with positive family history had autosomal recessive mode of inheritance. Many specific clinical signs were described that helps to diagnose hereditary muscle disorders with certainty. Calf hypertrophy was observed in DMD (100%), BMD (80%) and in some of the LGMD patients (20%). Conclusion: Hereditary muscle disorders are common among males than in females. Most of the patients with hereditary muscle disorders were in the age group of 10 to 20 years (2nd decade). Earliest age of onset in our study was 2 years (DMD). Most common hereditary muscle disorders was LGMD (57%) followed by FSHD (11.4%) and BMD (11.4%). Polyhill sign and scapular winging were seen in all our patients with FSHD, which is a characteristic finding in this disease. Specific clinical signs were less commonly noted in our patients with LGMD.

Keywords---Hereditary muscle disorders, clinical spectrum, LGMD, DMD.

Introduction

Myopathies are disorders in which a primary functional or structural impairment of skeletal muscle. In general, Muscle disorders are classified into hereditary and acquired disorders¹. Muscle disorders are differentiated from disorders involving motor neurons, peripheral nerves or neuromuscular junction, by their characteristic clinical and laboratory features². Therefore, the approach to a patient with a suspected muscle disease is to determine the correct site of the lesion from history and physical examination. Once localized to the muscle, the next step is to identify whether the myopathy is due to a defect in the muscle channel, muscle structure, or a dysfunction in muscle metabolism. Subsequently the cause of the myopathy is to be determined. This will help to decide on management and prognostication issues. We undertook this study of hereditary muscle disorders to identify the demographic profile and clinical spectrum, which will help in recognizing them early for adequate management with rehabilitation measures and for prognostication.

Aims and Objectives

The aim of the study is,

1. To study the demographic profile of patients with hereditary muscle disorders.

2. To study the clinical spectrum of hereditary muscle disorders.

Material and Methods

Study Centre: Institute of Neurology, Madras Medical College, Chennai.

Study design: Cross sectional study.

Study period: July 2018 to February 2019 (8 months).

Study Sample: 44 patients (Males-32, Females-12).

Inclusion criteria: Patients with clinical features suggestive of Hereditary muscle disorders.

Exclusion criteria: The following patients are excluded from the study,

- Patients with clinical features, electro diagnostic tests (NCV/EMG) suggestive of neuropathies or neuromuscular junction disorders.
- Patients with features suggestive of drug-induced myopathies.
- Patients with features suggestive of toxic myopathies.
- Patients with features suggestive of Endocrine myopathies.
- Patients with features suggestive of myositis (infective/ inflammatory).

Clinical Evaluation

Clinical evaluation of all patients were done with,

- ❖ Detailed history taking.
- ❖ Clinical examination.
 - i. General Examination with details about the presence of contractures, skeletal deformities, etc.
CNS Examination which included higher mental function, cranial Nerves, spinomotor system, reflexes, in coordination, sensory system, gait, cerebellar and extra pyramidal system examinations.
 - ii. Muscle testing which included examination of muscle bulk, tone, power, reflexes, muscle tenderness, identifying specific pattern of muscle involvement and other characteristic signs (eg. polyhill sign in FSHD).

Data Analysis

All the data were tabulated in Microsoft XL sheet, followed by analysis using SPSS software (version 20.0).

Results

Demographic Profile:

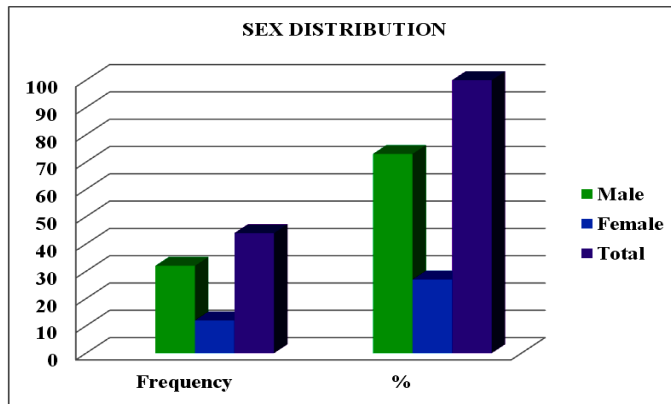


Fig. 1: Sex Distribution

Fig. 1 shows a total of 44 patients were included in our study, out of which 32 (72.7%) were males and 12 (27.3%) were females.

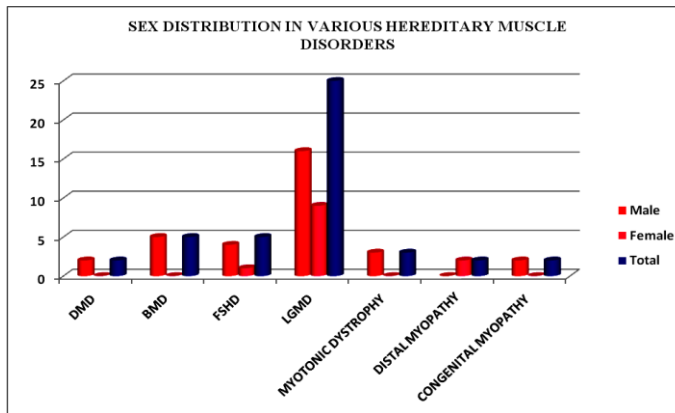


Fig. 2: Sex Distribution in Various Hereditary Muscle Disorders

Fig. 2 shows patients with BMD, all 5 (100%) were males. Among 5 FSHD among 25 LGMD patients, 16 (64%) were males and 9 (36%) are females, 4 (80%) were males and 1(20%) was female. 3 patients had Myotonic dystrophy. All 3 (100%) were males. Total of 2 had Distal Myopathy. Out of 5 and all 2 (100%) were females. 2 had Congenital Myopathy and all 2 (100%) were males. All 2 (100%) patients with DMD were males.

Table 1: Age Distribution of Patients with Hereditary Muscle Disorders

Diagnosis Of Muscle Disorders	Age Groups (Yrs)					Total	p<0.083
	1 – 10	11 – 20	21 – 30	31 – 40	41 – 50		
DMD (n = 2)	2	0	0	0	0	2	
BMD (n = 5)	3	1	0	1	0	5	
FSHD (n = 5)	1	2	0	1	1	5	
LGMD (n = 25)	3	11	6	4	1	25	

Myotonic Dystrophy (N = 3)	0	2	0	1	0	3
Distal Myopathy (N = 2)	0	0	2	0	0	2
Congenital Myopathy (N = 2)	0	2	0	0	0	2
Total	9	18	8	7	2	44

Table 1 shows among 25 patients with LGMD, 11 (44%) belong to the age group of 11-20 yrs, 6 (24%) to 21-30 yrs, 4 (16%) to 31-40 yrs, 3 (12%) to 1-10 yrs and 1 (4%) to 41-50. Out of 5 affected with FSHD, 2 (40%) belong to the age group of 11-20 yrs, 1 (20%) to 1-10 yrs, 1(20%) to 31-40 yrs, 1 (20%) to 41-50 yrs. In a total of BMD patients, 3 (40%) belong to age group of 1-10 yrs, 1 (20%) in the age group of 11-20 yrs and 1 (20%) in the age group of 31-40 yrs. Out of 3 with Myotonic dystrophy 2 (66.67%) belong to age group of 11-20yrs and 1 (33.33%) to 31-40 yrs. All 2 (100%) with Distal Myopathy belong to the age group of 21-30 yrs. All 2 (100%) with Congenital myopathy belong to the age group of 11-20 yrs. All 2 (100%) of DMD patients belong to age group of 1-10yrs. The mean age of the patients with muscle disorders was 24.38 years with Standard deviation (SD) 11.82 yrs.

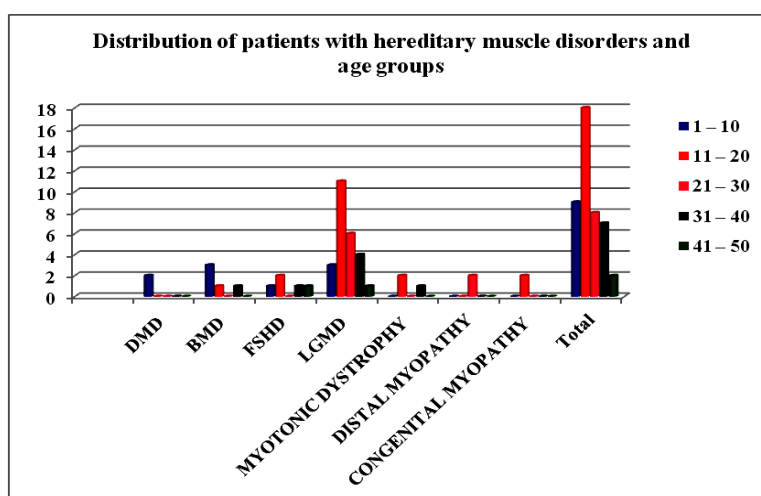


Fig. 3: Distribution of Patients with Hereditary Muscle Disorders and age groups

Clinical Spectrum:

Table 2: Distribution of Various Hereditary Muscle Disorders

Diagnosis of Hereditary Muscle Disorders	Frequency(N)	Percent (%)
DMD	2	4.55
BMD	5	11.36
FSHD	5	11.36
LGMD	25	56.81

Myotonic Dystrophy	3	6.82
Distal Myopathy	2	4.55
Congenital Myopathy	2	4.55
Total	44	100

Table 2 shows among the total of 44 patients, 25 were LGMD which accounts 57% of patients. 5 patients (11.4%) each in BMD and FSHD were observed. 3 patients (6.8%) had myotonic dystrophy. 2 (4.5%) patients each in DMD, Congenital myopathy and distal myopathy group were noted in our study.

Age at Onset of Disease:

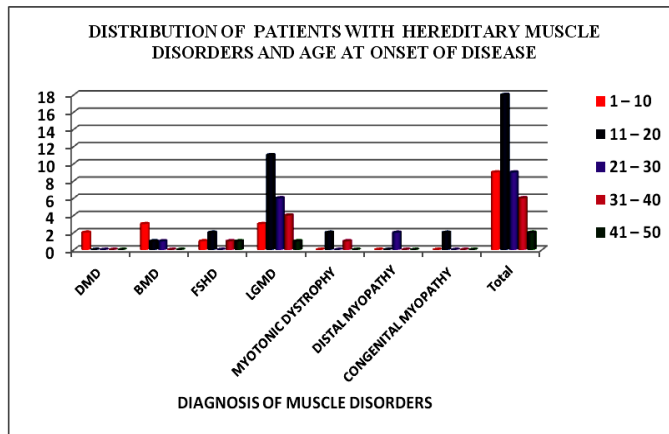


Fig. 4: Distribution of Patients with Hereditary Muscle Disorders and age at onset of Disease

Fig. 4 shows in a total of 25 patients with LGMD 11 (44%) had disease onset between 11-20yrs, 6 (24%) in 21-30yrs, 4 (16%) in 31-40yrs, 3 (12%) in 1-10yrs and 1 (4%) in 41-50yrs. Out of 5 affected with FSHD, 2 (40%) had disease onset between 11-20yrs, 1 (20%) in 1-10 yrs, 1 (20%) in 31-40 yrs and 1 (20%) in 41-50 yrs. Out of 5 patients with BMD, 3 (40%) had disease onset in the age group of 1-10yrs, 1 (20%) in 11-20yrs and 1 (20%) in 21-30 yrs. Out of 3 with Myotonic dystrophy, 2 (66.67%) had disease onset in the age group of 11-20 yrs and 1 (33.33%) in 31-40 yrs. All 2 (100%) patients with distal Myopathy had disease at onset in the age group of 21-30 yrs. All 2 (100%) with Congenital myopathy had disease at onset in the age group of 11-20 yrs. All 2 (100%) patients with DMD had disease of onset in the age group of 1-10 yrs. The mean age of onset of the disease in patients with muscle disorders was 19.31 yrs with Standard deviation (SD) 11.08 yrs.

Table 3: Distribution of Patients with Hereditary Muscle Disorders and Duration of the Disease

Diagnosis of Muscle Disorders	Duration of Disease (Yrs)				Total	p<0.574
	1 - 5	6 - 10	11 - 15	16 - 20		
DMD (n = 2)	0	2	0	0	2	
BMD (n = 5)	3	1	1	0	5	
FSHD (n = 5)	2	1	2	0	5	
LGMD (n = 25)	16	8	1	0	25	
Myotonic Dystrophy (N = 3)	2	1	0	0	3	
Distal Myopathy (N = 2)	2	0	0	0	2	
Congenital Myopathy (N = 2)	2	0	0	0	2	
Total	27	13	4	0	44	

Table 3 shows among 25 patients with LGMD, 16 (64%) had a duration of 1-5yrs, 8 (32%) of 6-10 yrs, 1 (4%) of 11-15 yrs. Out of 5 affected with FSHD, 2 (40%) were suffering for a period of 1-5 yrs, 1 (20%) for 6-10yrs and 2 (40%) for 11-15 yrs. Among 5 patients with BMD, 3 (40%) were suffering for a period of 1-5 yrs, 1(20%) for 6-10 yrs and 1 (20%) for 11-15 yrs. Out of 3 patients with Myotonic dystrophy, 2 (66.67%) had a duration of 1-5 yrs and 1 (33.33%) had duration of 6-10 yrs. All 2(100%) patients with distal myopathy were suffering for a period of 1-5 yrs. All 2 (100%) affected with Congenital myopathy were suffering for a period of 1-5 yrs. The 2 (100%) DMD affected person had been suffering from the disease for 6-10 yrs. The mean duration of the disease in patients with muscle disorders was 5.3 yrs with Standard deviation (SD) 3.76 yrs.

Table 4: Inheritance Pattern in Various Hereditary Muscle Disorders

Diagnosis of Muscle Disorders	Family History				Total	p<0.001
	Autosomal Recessive	Autosomal Dominant	X-linked Recessive	Not Clear		
DMD (n = 2)	0	0	2	0	2	
BMD (n = 5)	0	0	4	1	5	
FSHD (n = 5)	0	0	0	5	5	
LGMD (n = 25)	7	0	0	18	25	
Myotonic Dystrophy (N = 3)	0	2	0	1	3	
Distal Myopathy (N = 2)	0	1	0	1	2	
Congenital Myopathy (N = 2)	1	1	0	0	2	
Total	8	4	6	26	44	

Table 4 shows among 25 patients with LGMD, 18 (72%) had no or unclear family history and 7 (28%) had autosomal recessive inheritance. None of the 5 (100%) patients with FSHD, had family history. Among the 5 with BMD, 4 (80%) have XR pattern of inheritance and 1 (20%) had no family history. Out of 3 with Myotonic dystrophy, 2 (66.7%) had autosomal dominant type of inheritance and 1 (33.33%) had no family history. Among 2 with distal myopathy, 1 (50%) had autosomal dominant type of inheritance and 1(50%) had no family history. Out of 2 with congenital myopathy 1 (50%) had autosomal recessive type of inheritance and 1 (50%) had autosomal dominant type of inheritance. All 2 (100%) with DMD had XR type of inheritance. The distribution of the subjects with muscle disorders and type of their inheritance was found to be statistically significant ($p<0.001$).

Table 5: Distribution of the Subjects with Diagnosis of Hereditary Muscle Disorders and Symmetry of Weakness

Diagnosis Of Muscle Disorders	Weakness		Total	P<0.007
	Symmetrical (%)	Asymmetrical (%)		
DMD (n = 2)	2	0	2	
BMD (n = 5)	5	0	5	
FSHD (n = 5)	2	3	5	
LGMD (n = 25)	24	1	25	
Myotonic Dystrophy (N = 3)	3	0	3	
Distal Myopathy (N = 2)	2	0	2	
Congenital Myopathy (N = 2)	2	0	2	
Total	40	4	44	

Table 5 shows in a total of 25 patients with LGMD, 24 (96%) had symmetrical weakness and 1 (4%) had asymmetrical weakness. Out of 5 patients with FSHD, 2 (40%) had symmetrical weakness and 3 (60%) had asymmetrical weakness. All 5 patients with BMD had symmetrical weakness. All 3 (100%) patients with Myotonic dystrophy had symmetrical weakness. All 2 (100%) patients with DMD had symmetrical weakness. All 2 (100%) patients with distal Myopathy had symmetrical weakness. All 2 (100%) suffering from Congenital myopathy had symmetrical weakness. Distribution of subjects with diagnosis and pattern of weakness was found to be statistically significant ($p<0.007$).

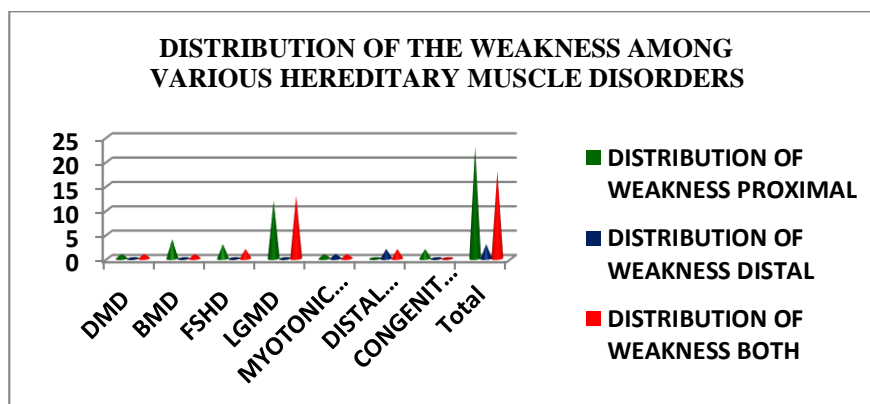


Fig. 5: Distribution of the Weakness among Various Hereditary Muscle Disorders

Table 6: Specific Clinical Signs

Clinical signs	DMD	BMD	LGMD	FSHD	Myotonic Dystrophy	Congenital Myopathy	Distal Myopathy
Calf Hypertrophy	2 (100%)	4 (80%)	5 (20%)	0	0	0	0
Gowers Sign	2 (100%)	2 (40%)	7 (28%)	0	0	0	0
Scapular Winging	0	0	5 (20%)	5 (100%)	0	0	0
Polyhill Sign	0	0	0	5 (100%)	0	0	0
Calf Atrophy	0	0	3 (12%)	0	0	0	1 (50%)
Diamond Quadriceps	0	0	4 (16%)	0	0	0	0
Hip abduction Sign	0	0	8 (32%)	0	0	0	0
Biceps Lump	0	0	4 (16%)	0	0	0	0
Valley Sign	1 (50%)	1 (20%)	1 (4%)	0	0	0	0
Contractures	1 (50%)	1 (20%)	4 (16%)	0	0	0	0
Hatchet Facies	0	0	0	0	2 (66.7%)	0	0
Myotonia	0	0	0	0	3 (100%)	0	0

Table 6 shows specific clinical findings found among various hereditary muscle disorders in our study are shown in the table 11. All 5(100%) Of patients with FSHD had polyhill sign and scapular winging. All 2(100%) of patients with DMD had gower's sign and calf hypertrophy. All 3 (100%) patients with myotonic dystrophy had percussion or grip myotonia. Biceps hump (16%), Diamond

quadriceps (16%), hip abduction sign (32%), calf atrophy (12%) were the specific signs noted in our LGMD patients.

Discussion

Hereditary muscle disorders are more common than acquired myopathies. Clinical suspicion, correct approach and appropriate investigations will lead us to an accurate diagnosis. Demographic and clinical spectrum of hereditary muscle disorders are discussed in the following section.

In our study with a total of 44 patients, 32 (72.7%) were males and 12 (26.3%) were females. In LGMD out of 25 patients, 16 (64%) were males and 9 (36%) were females, whereas in a study by **Meena et al**², it was 54% and 46% for males and females respectively. All 2 (100%) patients with congenital myopathy were females.

In a total of 44 patients with hereditary muscle disorders, 40 (91%) were muscular dystrophies. LGMD is the most common hereditary muscle disorders in our study (57%) and DMD is found in only 5%, which is in contrast to a study by **Das et al**³, where both DMD (30%) and LGMD (29.2%) were equally prevalent. This gross difference in prevalence in our study could be due to the fact that most of the DMD patients possibly were evaluated and treated by paediatric neurologist whereas our centre is an adult referral hospital and so only, less number of patients were referred here for neurological consultation. According to another Indian study (**Khadhilkar S V et al.**)⁴, LGMD formed the most common hereditary muscle disorder, which is consistent with our study.

The age distribution in our patients showed that 20% of the patients were in the age group of less than 15 years which is in line with a study by **Buchthal F et al**⁵, in which 25% of the myopathic patients were in that age group. Majority of our patients were young (2nd decade). No patients with hereditary muscle disorders are found beyond 5th decade in our study. Earliest age at onset in our study was 2 years (DMD) and late age at onset was 50 years (FSHD). All 2 (100%) patients with congenital myopathy had age at onset in 3rd decade. This shows that our patients with congenital myopathy could be the milder adult onset variants. All 2 (100%) patients with distal myopathy had early age onset (2nd decade), one of the patient had autosomal dominant mode of inheritance (Laing syndrome). The other patient had no clear family history, without neck weakness and the biopsy showed fibre necrosis without rimmed vacuoles and so she could be a case of miyoshi myopathy. This shows that the distal myopathy (Laing or Miyoshi) are not uncommon in our population.

Among all patients with muscular dystrophies (40), only 3 (7.5%) were myotonic dystrophy which correlates with another Indian study (8%) by **Gouridevi et al**⁶ FSHD constitutes 12.5% of patients with muscular dystrophies, which is in contrast to other Indian studies where only 2.3% and 1.3% were seen by **Srinivas et al**⁷ and **Das et al**² respectively. congenital myopathy and distal myopathy were diagnosed in 2 (4.5%) patients each, equal to the incidence of DMD (4.5%) which is consistent with the incidence from a study by **Nonaka I et al**⁸.

Among 44 patients only 4 (9.1%) patients had asymmetric weakness. As comparable to many previous studies, asymmetric weakness was more common in FSHD patients (6.8%). In our study, asymmetric muscle weakness was also noted in a patient with LGMD (2.3%) which was also observed in previous study by **Khadilkar SV et al**⁴ (42%).

Most of our patients with positive family history had autosomal recessive mode of inheritance and this could be due to the commonly practiced custom of consanguineous marriage in our population. Next common mode of inheritance was X-linked recessive followed by autosomal dominant pattern. Among LGMD 28% of patients had AR pattern and no patients had AD pattern of inheritance, which correlates well with a previous Indian study by **Khadilkar et al**⁴.

Weaknesses involving both upper and lower limbs were commonly seen in our patient (79.5%) which is consistent with many previous studies. This could possibly be due to the fact that most of our patients seek medical advice only late in the illness. Many specific clinical signs were described that helps to diagnose hereditary muscle disorders with certainty. Calf hypertrophy was observed in DMD (100%), BMD (80%) and in some of the LGMD patients (20%). In contrast to our study, 53.8% of patients with LGMD (Sarcoglycanopathies) had calf hypertrophy in a study by Meena et al, Gowers sign was seen in DMD (100%), BMD (40%) and in 28% of patients with LGMD. This sign along with calf hypertrophy in young boys are diagnostic of DMD (**Mansur et al**)⁹. Contractures in patients with muscular dystrophy is well described in literature which was also noted in our patients. Contractures were seen in DMD (50%), BMD (20%) and in LGMD (16%) which correlates with a study by **Mansur et al**⁹.

All 5 (100%) patients with FSHD had polyhill sign which is due to a differential wasting in certain muscles with relative preservation of muscle bulk around shoulder girdle. This is specifically seen in patients with FSHD (**Pradhan et al**)¹⁰. Winging of scapula (Angel wing appearance) was also seen in all 5 (100%) of patients with FSHD, but this was also noted in some LGMD patients. Atrophy of calf muscle s(12%),Biceps lump(due to differential wasting in biceps) 16% and Diamond quadriceps (16%) were also noted in our patients with LGMD, which has been described in patients with LGMD (dysferlinopathy) by **Pradhan et al**¹⁰.

Hip abductor sign with splaying of legs while getting up from squatting, which occurs due the profound weakness of hip adductors with preserved hip abductors is well documented to occur in patients with LGMD like sarcoglycanopathy (**Khadilkar et al**)⁴. This sign was seen in 8 (32%) patients with LGMD in our study. Hip abductor sign is helpful in differentiating LGMD from DMD/ BMD, since in the later hip abductors, quadriceps and iliopsoas are involved earlier with severe degree of weakness as compared to hip adductor/ hamstrings involvement in LGMD. The specific signs that are described in literature were also noted in our study, but only in a lesser number of patients.

Valley sign (due to the prominent wasting in posterior axillary muscles with relatively preserved deltoid and infraspinatus) described by Pradhan et al, was observed in 1 (50%) patient with DMD, 1 with BMD (20%) and 1 with LGMD (4%) in our study.

Conclusion

In conclusion, the following observations were made from our study,

- Hereditary muscle disorders are common among males than in females.
- Most of the patients with hereditary muscle disorders were in the age group of 10 to 20 years (2nd decade).
- No patients with hereditary muscle disorders were found beyond 5th decade in our study.
- Most common hereditary muscle disorders was LGMD (57%) followed by FSHD (11.4%) and BMD (11.4%).
- Earliest age of onset in our study was 2 years (DMD).
- Most common pattern of involvement was proximal limb girdle pattern with all DMD, BMD, LGMD, Congenital myopathy patients in that group.
- Polyhill sign and scapular winging were seen in all our patients with FSHD, which is a characteristic finding in this disease. Specific clinical signs were less commonly noted in our patients with LGMD.
- Hence, a structured clinical approach focusing on pattern of muscle involvement and on specific clinical signs along with investigations like serum CPK, EMG and Muscle biopsy, it is possible to make an accurate early diagnosis in hereditary muscle disorders, prognosticate and manage them appropriately.

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