LIMB GIRDLE MUSCULAR DYSTROPHY IN EARLY CHILDHOOD- CLINICAL HETEROGENEITY AND CLUE TO EARLY DIAGNOSIS

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ABSTRACT

BACKGROUND

The aim of the study is to evaluate the clinical profile of early-childhood Limb Girdle Muscular Dystrophy (LGMD) and to determine the phenotype and age of manifestation.

MATERIALS AND METHODS

It is a retrospective, descriptive, observational study; data collected by hospital-chart review, in University Hospital of South India. Children with muscle-biopsy proven children with dystrophy, with symptom-onset of less than or equal to five years were included.

RESULTS

Eight had onset at or below two years, fourteen between two to five. Of early-onset cases, seven did not have definite referral diagnosis presented with delayed milestones. Phenotypically all were Duchenne Muscular Dystrophy (DMD). Other types of LGMD were not recognized.

CONCLUSION

Early diagnostic suspicion of muscular dystrophy, (especially DMD, which is having genetic implications and treatable to limited extent), should be emphasized in those with delayed milestones.

Neonatal screening of DMD is not recommended universally. It is important to have clinical suspicion very early in life, as DMD presents as delayed milestones. Serum CK estimation helping in diagnosis, can be followed by genetic testing or muscle biopsy with immunostaining. Calf hypertrophy adds weightage to diagnostic suspicion. Early diagnosis will contribute to genetic counselling and treatment will slow disease progression, improve quality and life expectancy.

KEYWORDS

Limb Girdle Muscular Dystrophy, Duchenne Muscular Dystrophy, Clinical Heterogeneity, Onset-Age, Delayed Milestones.

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BACKGROUND

Limb Girdle muscular dystrophies are heterogeneous group of genetic disorders, causing shoulder and pelvic girdle weakness, manifesting in children or adults. It could be autosomal recessive, dominant or X-linked recessive. Duchenne muscular dystrophy (DMD) is the most common, muscular dystrophy, which is X-linked affecting 1in 3500[1] live births.

Autosomally inherited dystrophies are rare, has slower progression and can occur at any age. While Sarcoglycanopathy, Fukutinopthy, Titinopathy etc., are recessive; Laminopathy, Caveolinopathy and Transportinopathy are dominant.[2] Sarcoglycanopathy, the commonest, forms 26.4% of all LGMD;[3] and 3% of Childhood autosomal LGMD.[4] DMD is common than other dystrophies, manifests within 5 years (2-5 years) while Sarcoglycanopathy, after six years.[2] DMD progresses fast leading to wheelchair dependency by 12 years while Sarcoglycanopathy patients are mobile till third decade. Early initiation of steroid therapy can prolong ambulation by around three years[4] for DMD, while for Sarcoglycanopathy and other autosomal dystrophies, treatment is essentially supportive.

DMD should be recognized at the earliest, when they present as delayed milestones. Classification of LGMD is basically clinical, based on inheritance pattern and clinical expression. Exact subtyping of LGMD is difficult due to phenotypic heterogeneity, but is useful for predicting prognosis and genetic counselling. At peripheral level, identification and referral of LGMD (DMD); first by screening with CK and genetic study, and biopsy with immunostaining, if needed should be done at the earliest,[4] when child presents with delayed milestones.

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In DMD, steroid therapy had extended period of mobility for around three years or more.[5] Mortality due to respiratory causes has improved to 17.7 years for non-ventilated and 27.9 years, for ventilated; cardiac mortality improved to 19.6 years.[6]

Objective

Describe clinical profile and heterogeneity in presentation of LGMD phenotype in very young children.

MATERIALS AND METHODS

Retrospective descriptive study using data collected by reviewing hospital charts was done. Using specific codes for muscular dystrophy, children fulfilling diagnostic criteria were selected. Twenty-two subjects were included.

Inclusion Criteria

1. Proximal muscle weakness before five years.
2. Creatinine kinase elevated ten times at evaluation.
3. Electromyographic findings consistent with diagnosis of myopathy.
4. Skeletal muscle biopsy consistent with diagnosis of muscular dystrophy.

The cohort evaluated at Thiruvananthapuram, were residents of South India. Investigator personally evaluated all who were able to travel to Centre. Others were evaluated by sending performa to them. Details of specific milestones achieved and other features like dyspnea, orthopnea and cardiomegaly, and GIT symptoms like abdominal pain, vomiting, ileus and faecal impaction were enquired.

Details of investigations like muscle enzymes, CK (Creatinine Kinase), LDH (lactate dehydrogenase) EMG and Muscle biopsy and ECHO, ECG and X-ray chest were collected.

Examination findings of sisters, brothers, mothers, maternal uncles, calf hypertrophy, contractures, and weakness of hip extensors, adductors, abductors, quadriceps, brachioradialis and neck-flexors were collected.

Statistics

Descriptive statistics were used to summarize data.

RESULTS

There were twenty-two boys, who can be divided into two groups;

Group-1: early-onset symptoms (before two years); eight of them, seven had developmental delay and one abnormal gait. (Table 1).

Group-2: onset-age after two years; fourteen in this group. Five had inability to run, four had falls, four had difficulty in getting up from squat, and two had mental sub normality (Table 2).

Sl. No.	Onset in Years; Symptoms	Walking Assisted	Chair Bound	Upper Limbs Affected
1.	<1.5y; delayed psychomotor development	8 years	8.5 years	7.5 years
2.	2y; abnormal gait	8 years	Walks with support	Upper limbs unaffected
3.	2y; psychomotor delay	10years	10.5 years	8years
4.	2y; motor delay	6.5 years	8 years	8 years
5.	1y; psychomotor delay	9 years	Walking	8 years
6.	2y; motor delay	8.5 years	9 years	9 years
7.	1.5y; motor delay	7 years	_9years	9 years
8.	1.5y; motor delay	8.5 years	9 years	9.5 years

Table 1. Patients with Onset-Age <2 years

None of eight patients had cardiac, cardio-respiratory, GIT symptoms or cardiomyopathy.

Sl. No.	Age of Onset; Symptom	Walks Assisted	Chair Bound	UL Affected	Cardiac/Cardio-Resp. Symptom	Cardiomyopathy	Sibling Affected
1.	4.5y; falls	8.5 yrs.	9.5 yrs.	8.5 yrs.	no	no	yes
2.	4.5y; unable to run	10 yrs.	11.5 yrs.	7 yrs.	no	yes	no
3.	4.5y; falls	10 yrs.	walks	8.5 yrs.	no	yes	no
4.	5y; unable to climb up	10 yrs.	12 yrs.	11 yrs.	Dyspnea; respiratory infection	no	yes
5.	4.5y; Falls; unable to run	9 yrs.	12 yrs.	10 yrs.	no	no	yes
6.	5y; falls	9 yrs.	12 yrs.	11 yrs.	no	no	yes
7.	5y; falls	10 yrs.	11 yrs.	10 yrs.	no	no	no
8.	3y; not ascend stairs	Walks by 8 yrs.	walks	no	no	no	no

9.	4.5y; unable to get up from squat	10 yrs.	12 yrs.	10 yrs.	no	no	no
10.	4.5y; unable to get up from squat	8.5 yrs.	10 yrs.	9 yrs.	no	no	no
11.	4y; unable getting up from squat	10 yrs.	10.5 yrs.	9 yrs.	Death at 15 yrs. of pneumonia	no	no
12.	3y; unable to run	8 yrs.	10 yrs.	8.5 yrs.	no	no	no
13.	5y; unable getting up from squat	9.5 yrs.	10 yrs.	9 yrs.	Dyspnea with respiratory infection	No	no
14.	3y; falls	9 yrs.	10 yrs.	9 yrs.	no	no	No

Table 2. Patients with Onset-Age >2 Years

Fifteen had referral diagnosis of DMD. Referral was without definite diagnosis for early onset group (7/8), pediatricians referred ten, of which four were for developmental delay; 4/10(40%), and general practitioner five, three were for delayed milestones, 3/5(60%). Of children referred for developmental delay, four were for motor and three for psychomotor delay.

All had skeletal deformities irrespective of the group. Exaggerated lumbar lordosis was first sign to appear. Advancing age increased deformities. Scoliosis occurred by eleven years. (Table-3)

Sl. No.	Signs	No. of Patients	Youngest Age
1.	Exaggerated lumbar lordosis	22	3.5 yrs.
2.	scoliosis	10	9 yrs.
3.	kyphosis	6	9 yrs.
4.	Winging scapula	4	10 yrs.
5.	All deformities	4	10 yrs.

Table 3. Skeletal Deformities

Tendo-Achilles contracture was present in all. Oldest had contractures of all joints, ankle, hip knee and elbow; knee joint contracture occurred when child lost ability to walk by 12 years and hip by 13 years. (Table-4)

Sl. No.	Contracture	No. Affected	Youngest Age
1.	Tendo-Achilles	22	3.5 yrs.
2.	Hamstrings	5	10 yrs.
3.	Ilio-psoas	3	10 yrs.
4.	Biceps	2	14 yrs.

Table 4. Contractures

All had calf muscle hypertrophy; deltoid, infraspinatus, supraspinatus, biceps and triceps were also hypertrophied (Table-5)

Muscles	No. of Patients
Calf	22
EDB	14
Deltoid	12
Infraspinatus	6
Supraspinatus	6
Biceps	4
Triceps	3

Table 5. Muscle Hypertrophy

Age	<9 years		>9 years	
Serum CPK values	>7,500	<7,500	>7,500	<7,500
Number of Patients	9	3	2	8

Table 6. Age and CPK Values

All had Glutei wasting; quadriceps, hamstrings and pectorals were variably wasted.

Glutei weakness was severe in 20, followed by quadriceps, while adductors had good power. Upper limbs were involved late (after seven years of onset), Pectorals, brachioradialis, biceps and triceps were weak.

Cardio-respiratory symptoms of dyspnea, cough and frequent respiratory infections were seen in two. Features of cardiomyopathy was found in three by investigations, of which one was asymptomatic. One patient died of cardiorespiratory failure at 14.5 years and another sibling had sudden cardiac death at age of 10 years.

None had gastrointestinal symptoms.

Before nine years patients had higher CPK values, after nine, had lower values, 9000-14000 and 3000-8000 respectively (Table-5).

DISCUSSION

Major causes of LGMD in children are DMD and sarcoglycanopathy which has overall similarities, but significant differences. Sarcoglycanopathy is rare, has age of

onset after six, normal cognition, cardiac sparing, slower progression enabling ambulation till second or third decade,[2,7,8] with hip-abduction sign due to selective involvement of adductors as compared to abductors.[2,4]

Phenotype of subjects in present series was DMD. There are different clinical manifestations of DMD, depending on type of mutations and consequent absence of dystrophin.[9,10,11] It could be delayed motor or psychomotor milestones to motor power regression in form of proximal muscle weakness or disease progressing to being chair-bound in early second decade to milder variants like Becker muscular dystrophy, intermediate muscular dystrophy causing ambulation beyond 13 years, isolated quadriceps myopathy, isolated cardiac involvement, cognitive dysfunction and some females manifesting milder disease due to skewed X-chromosomal inactivation.[11]

Clinical heterogeneity in DMD is described by Isabelle et al.[12] She described four distinct cognitive and motor patterns of onset and progression: - 1) Early infantile onset, affecting both cognition and muscle power severely, 2) Classical with intermediate severity, 3) Moderate, pure motor with normal cognition and 4) severe pure motor DMD. In current series, only two groups of patients could be recognized, early onset before two years and late onset after two years. Early onset had involvement of cognitive and motor functions in three subjects, while pure motor function involvement was there for five.

Early diagnosis can be made by recognizing different presenting symptoms.[13] Early treatment initiation with steroids,[14] newer drugs and other supportive care, will improve quality of life and life expectancy.[6] Steroids like Deflazacort or prednisone reduces mortality. It improves muscle strength, pulmonary function, delay onset of cardiomyopathy and reduces the need for scoliosis surgery.[14]

In a child with limb girdle syndrome DMD should be suspected[9] if family members are affected. If parents are unaffected, DMD should be suspected when child has not started to walk before 18 months or Gower's sign is positive in child below 5 years or unexpected elevation of transaminases irrespective of age.

Life expectancy at 20 years has improved from 20% to 60% over the last three decades, with drugs, supportive care, surgical corrections, appliances and treatment of respiratory failure. Quality of life and longevity of patients have improved with multidisciplinary care.[6,9]

CK levels are sensitive than clinical examination in suspecting DMD[14] Serum CK levels is elevated in very young patients with DMD and decreases as age advances[15] reflecting muscle injury. CK levels indicate muscle degeneration correlating with pulmonary function[16] CK levels was higher in patients less than 9 years compared to those above 9 years of age, correlating with functional levels than age.[12] Drugs like steroids improve CK levels and is used in trials to monitor drug efficacy.[17]

In early onset disease, loss of ambulation occurs early. On suspecting DMD, diagnostic possibility could be strengthened by presence of calf hypertrophy. Serum CK[18,19] is the best screening tool. Early onset group presented with delayed milestones, either psychomotor or motor milestones, causing misdiagnosis.

One of the drawbacks of study was lack of immunostaining and genetic studies, when possibility of sarcoglycanopathy and other autosomally inherited dystrophies could be excluded. Only males are afflicted here, whereas in autosomal muscular dystrophies, both males and females will be equally affected[2] Onset starting in proximal muscles with very late distal involvement, rapid progression of disease, leading to wheelchair dependency by 12 years, selective weakness of abductors, quadriceps and early involvement of upper limb muscles especially deltoid adds to diagnostic certainty of DMD. Onset –age less than five years, lack of consanguinity also contributes to diagnostic certainty of DMD.

The current diagnostic workup of DMD screening, identifies children only after latent symptomatic period of 3 to 5 y, diagnosing them by around four yrs. This denies precious time for offering life changing interventions.[20] Hence until, neonatal DMD screening is implemented, responsibility rests on each clinician who is concerned with children's well-being to be on look-out of DMD.[21]

What is Known?

Delayed diagnosis of DMD is an issue world-wide.

Age of diagnosis continues to be 5yr; even though most children are symptomatic by 2y 9m and diagnostic delay is taking toll on family even up to extent of having second affected child.[22]

What is Added?

Developmental delay, both motor and global occur in DMD. Though CK is done, as an investigation for developmental delay, till now, DMD is not considered as an aetiology with necessary gravity.[23]

DMD has to be born in mind as aetiology for developmental delay which needs definite exclusion, by CK and genetic testing, if needed, till neonatal screening for DMD is approved.

CONCLUSION

All clinicians taking care of children should be aware of the fact that Duchenne Muscular Dystrophy can manifest as developmental delay, both psychomotor and motor. Conversely, all children with developmental delay should be considered to be having Duchenne Muscular Dystrophy and screened by serum Creatine Kinase, confirmed by genetic testing enabling DMD to be diagnosed at earliest; which will help the child with improved quality, expectancy of life, till definitive therapy or neonatal screening is available.

Duchenne Muscular Dystrophy, a lethal muscular dystrophy of childhood has diagnostic, management and genetic counselling issues. It is imperative to be on look-out to prevent inherited DMD so that it could be reduced to those caused by mutation, which till date is not tackled upon. To this end paediatricians and general practitioners should be made aware of its heterogeneous presentation even in very early years of life.

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