ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 09 | September - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIAGNOSTIC DILEMMA IN ERA OF GENETIC TESTING: CONGENITAL MYOPATHY VS LIMB GIRDLE MUSCULAR DYSTROPHY

Paediatrics

Dr. Payal Ladda Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, (Resident).

Dr. Nikita Shah* Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, (Assistant Professor). *Corresponding Author

Dr. Yashwant Gabhale Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, (Additional Professor).

Dr. Radha Ghildiyal Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, (Professor and Head).

ABSTRACT

Congenital myopathies are heterogenous group of muscular disorder that present since birth but onset may be delayed, until early childhood. Limb girdle muscular dystrophy (LGMD) are genetic conditions that present with progressive primary muscle weakness due to loss of muscle fibre. We report a patient, who had clinical features of both myopathy and muscular dystrophy. Here we report a case girl in middle childhood,1st born of 3rd degree consanguinity with complaints of toe walking, gradually progressive difficulty in getting up from sitting position & bony protrusion over chest. She had elongated myopathic facies, atrophy of all skeletal muscles with dynamic contracture of bilateral lower limb causing equinus & pes cavus deformity. On evaluation, serum creatine phosphokinase was low normal, electromyography/nerve conduction velocity study showed decreased motor unit action potential in both upper limb and lower limb. On genetic study, genetic mutation was present for both congenital myopathy & LGMD.

KEYWORDS

crumb rubber, utilization, compressive strength, low cost, sustainable

INTRODUCTION

The term congenital myopathy refers to a group of clinically, genetically and histologically heterogeneous diseases that mainly affect muscle tissue. Different genes have now been identified as associated with the various phenotypic and histological expressions of these disorders, and in recent years, because of their unexpectedly wide genetic and clinical heterogeneity, next-generation sequencing has increasingly been used for their diagnosis.[1]

Clinical phenotype, in isolation, is insufficient for distinguishing between the different types of congenital myopathy, as it is often not specific, consisting of hypotonia and weakness present at birth or appear in infancy.[2] Although the precise epidemiology of congenital myopathy is not known, it has an estimated incidence of around 1:25,000, and has been reported to account for 14% of all cases of neonatal hypotonia.[3]

Patients with congenital myopathy have facial features secondary to muscle weakness, associated with a high arched palate, micrognathia and pectus carinatum or excavatum, the latter resulting from chest muscle hypotonia. The most common form, however, is less severe, being characterized by weakness of the limbs, trunk and facial muscles, and slowly progressive disease course. Although children affected by this form of myopathy develop muscle contractures and high-arched feet, most are able to walk.

Due to the heterogeneity of limb girdle muscular dystrophy (LGMD) and the lack of diagnostic specificity, estimates of prevalence for all forms of LGMD have ranged from 1 per 14500 to 1 per 123000 populations.[4]. Helpful clinical features that help to differentiate the various subtypes of LGMD include: predominant upper girdle weakness, disproportionate respiratory muscle involvement, distal weakness, hip adductor weakness, 'biceps lump' and 'diamond on quadriceps' sign, calf hypertrophy, contractures and cardiac involvement.

Herein we would like to discuss a child with genetic mutation for both muscular dystrophy and myopathy (homozygous for both). On detailed evaluation, child had clinical features of both, causing diagnostic dilemma.

CASE STUDY:

A 9 years old girl, born of 3rd degree consanguineous marriage, brought by grandmother, with toe walking since 2 years of age, bony protrusion over chest since last 4 years with progressive difficulty in sitting up from supine position, over last 2 years. Birth and antenatal history were uneventful. History of gross motor developmental delay present with walking achieved after 2 years of age, however child had toe walking. Milestones before this were appropriate for age. (Neck holding at 3 month and sitting without support at 9 month of age). At present child was able to walk- but had wide based gait, toe walking. Fine motor, social and language milestones were appropriate for age. On examination, child was severe thin (Body mass index-10.63 kg/m2) with normal head circumference (51.2cm). Child had high arched palate with elongated facies. All upper limb as well as lower limb muscle appeared atrophic including hypothenar muscles and gowers sign was positive. Dynamic contractures were present bilaterally at ankle joint and bilateral equinus with pes cavus deformity (figure 1) present. Figure 2 shows pectus carinatum deformity. All deep tendon reflexes were depressed and superficial reflexes present. No other family history of similar illness, except 1.5-year-old, younger sister -who has gross motor development delay. Serum Creatine kinase was borderline low (24.7 U/L). 2D echocardiography was normal and chest X ray (lateral view-figure 3) was suggestive of pectus carinatum. MRI Brain & Spine screening was done which did not show any abnormality. Clinically muscular disorder was suspected. Electromyography/nerve conduction study revealed decreased motor unit action potentials with early recruitment in tibialis anterior, vastus medialis, bicep and flexor digitorum intermedialis primarily s/o muscle disease. Genetic study, as shown in Figure 4, revealed two homozygous mutations - TPM3 s/o congenital myopathy and POMGNT2 s/o Limb girdle muscular dystrophy with dystroglyconopathy.

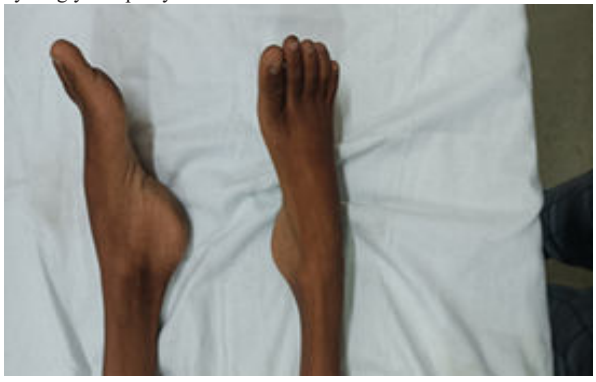

Figure 1: *Bilateral Equinus With Pes Cavus*

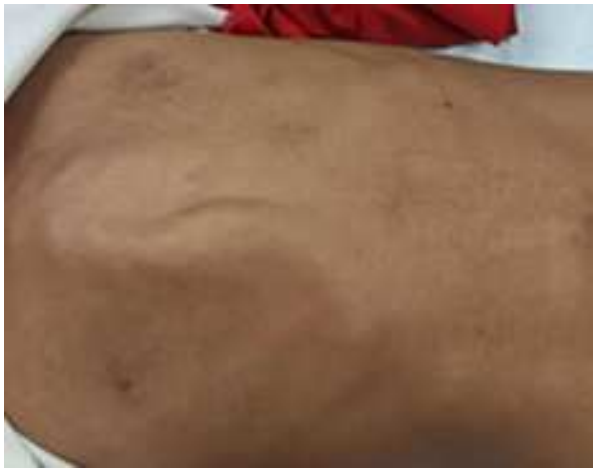

Figure 2- *Pectus Carinatum*

Figure 3: *x ray chest - pectus carinatum*

Table No 1:- Muscle Charting

Joint	Movement	Right	Left
Shoulder Joint	Flexion	3/5	3/5
	Extension	3/5	3/5
	Abduction	2/5	2/5
	Adduction	4/5	4/5
Elbow joint	Flexion	3/5	3/5
	Extension	3/5	3/5
Wrist	Palmer flexion	4/5	4/5
	Dorsi flexion	4/5	4/5
	Side to side movement	4/5	4/5
Hand grip		4/5	4/5
Hip Joint	Abduction	2/5	2/5
	Adduction	3/5	3/5
	Flexion	3/5	3/5
	Extension	3/5	3/5
Knee joint	Flexion	3/5	3/5
	Extension	3/5	3/5
	Abduction	3/5	3/5
	Adduction	3/5	3/5
Ankle joint	Inversion	3/5	3/5
	Eversion	2/5	2/5
	Planer flexion	3/5	3/5
	Dorsal Extension	3/5	3/5
Neck	Flexion	2/5	2/5
	Extension	3/5	3/5
	Side to side movement	4/5	4/5

Table 2: Investigations:

Investigation	Result
Complete blood count	Hb-11.3 gm% /Hct- 38.2/TLC 11670/cumm /Plt-365K/cumm/N57%/ L37% MCV-89.4cumm/MCH 26.4pg/MCHC-29.6%
Liver function test	AST/ALT-55/27 U/L
Renal function test	12/0.6 mg/dl
Serum electrolyte	137/3.9 meq/L
Thyroid profile	FT3-3.20 (N=2.02-4.43)/ FT4-1.37 (N=0.93-1.70)/S.TSH-2.31 (N=0.60-4.84)
S. creatine kinase	24.3 U/L (N=38-174)
2 d echocardiography	No abnormality detected, Ejection Fraction- 55-60%
MRI brain with spine screening	No abnormality detected
Electromyography and Nerve conduction study	Electromyography study showed decreased Motor Unit Action Potential (MUAP) & early recruitment in Rt Tibialis anterialis, vastus medialis, biceps and flexor digitorum profundus thus finding was primarily muscle disease s/o myopathy.

Gene[a] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance
TPM3 (-) (ENST00000651641.1)	Exon 10	c.856T>A (p.Ter286LysextTer57)	Homozygous	Congenital myopathy-48 (OMIM#609284)	Autosomal recessive
POMGNT2 (-) (ENST00000344697.3)	Exon 2	c.1070G>A (p.Arg357His)	Homozygous	Limb- girdle muscular dystrophy-dystroglycanopathy (type C8; MDDGC8) (OMIM#618135)	Autosomal recessive

Figure 4: Exome sequencing report: Child with congenital myopathy with limb girdle muscular dystrophy in first decade of life both with autosomal recessive mode of inheritance.

DISCUSSION:

A correct diagnostic approach requires the integration of data from: clinical evaluations (including a detailed family history), muscle biopsy (including histological, immunohistochemical and electron microscopy examinations) and muscle MRI. Serum creatine kinase measurement and electromyography, which are very useful diagnostic tools in other neuromuscular disorders, are not particularly helpful for diagnosing congenital myopathy, given that creatine kinase levels are usually normal or mildly elevated, while electromyography can either be normal or, at most, show myopathy-like findings or neuropathic changes. Today, thanks to the possibility of combining genetic data (including the dataset obtained by massive analysis of multiple genes with methods of next-generation sequencing, NGS) with clinical and morphological findings and MRI results, our chances of achieving a precise diagnosis has increased.

Considering clinical features neuromuscular disorder was suspected in our case. Symmetrical involvement of shoulder and hip girdle with muscle atrophy was suggestive of limb girdle muscular dystrophy (Girl child), however was no pseudo-hypertrophy. Hypotonia, bony abnormalities in form of scoliosis and pectus carinatum were suggestive of congenial myopathy. As there were mixed picture of both- whole exome sequencing was sent for definitive diagnosis.

Table No 3:- Overlapping Features Of Both Disease In Our Patient

Congenital Myopathy	Limb Girdle Dystrophy
Hypotonia	Muscle Atrophy
Profound generalized weakness	Symmetrical weakness
Scoliosis	Tibialis anterior spared
Contracture	Winging of scapula
Dysphagia	
Pectus carinatum	

In the era of genetic study and advanced diagnostic techniques, differentiating between congenital myopathy and limb-girdle muscular dystrophy can present a diagnostic dilemma. Both conditions involve muscle weakness and may have overlapping clinical features, making it challenging to establish an accurate diagnosis based solely on clinical presentation.

Congenital myopathy refers to a group of genetic muscle disorders characterized by muscle weakness and hypotonia (reduced muscle tone) that are present from birth or early infancy. These conditions are caused by defects in proteins involved in muscle contraction, leading to impaired muscle function. Congenital myopathies can display various patterns of inheritance, including autosomal recessive, autosomal dominant, or X-linked. On the other hand, limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of genetic muscle disorders that primarily affect the muscles around the limbs and the shoulder and hip girdles. LGMD typically manifests during

late childhood, adolescence, or adulthood, although some forms may present earlier in life. It is characterized by progressive muscle weakness and wasting, with some subtypes showing additional features such as cardiac involvement or respiratory impairment.

To differentiate between congenital myopathy and Limb girdle muscular dystrophy, several diagnostic approaches can be employed:
1. Clinical Evaluation: A thorough physical examination, including assessment of muscle strength, reflexes, and contractures, helps identify distinguishable features. However, reliance solely on clinical findings may not be sufficient to make a definitive diagnosis.
2. Genetic Testing: Next-generation sequencing (NGS) techniques have revolutionized the diagnosis of genetic muscle disorders.
3. Muscle Biopsy: Histological analysis of a muscle biopsy specimen can provide valuable information. Features such as structural abnormalities, fibre type disproportion, or the presence of nemaline rods suggest congenital myopathy. In contrast, dystrophic changes, including fibre necrosis, regeneration, and fibrosis, are typically observed in LGMD.
4. Electromyography (EMG) and Nerve Conduction Studies: These tests evaluate the electrical activity of the muscles and nerves. EMG findings in congenital myopathy are typically myopathic, indicating muscle involvement. In LGMD, neurogenic findings may be present due to secondary denervation and reinnervation.
5. Muscle Imaging: Magnetic resonance imaging (MRI) or computed tomography (CT) scans can provide insights into muscle involvement patterns. Certain patterns, such as selective involvement of the shoulder or hip girdles in LGMD, may support the diagnosis.

Overall, the distinction between congenital myopathy and limb-girdle muscular dystrophy requires a multidisciplinary approach combining clinical evaluation, genetic testing, muscle biopsy, and supplementary investigations.

We reported this case as genetic test was suggestive of mutations for two different syndrome and on detailed analysis patient had overlapping features of both diseases. (Table 3)

In conclusion, genetic studies are invaluable in the field of congenital myopathy as they provide essential information for diagnosis, classification, prognosis, and potential therapeutic targets. By unravelling the genetic underpinnings of congenital myopathy, these studies contribute to our understanding of the disease and pave the way for personalized approaches to patient care.[6]

REFERENCES

[1] Cassandrini D, Trovato R, Rubegni A, Lenzi S, Fiorillo C, Baldacci J, Minetti C, Astrea G, Bruno C, Santorelli FM; Italian Network on Congenital Myopathies. Congenital myopathies: clinical phenotypes and new diagnostic tools. Ital J Pediatr. 2017 Nov 15;43(1):101. doi: 10.1186/s13052-017-0419-z. PMID: 29141652; PMCID: PMC5688763
[2] North, Kathryn N et al. "Approach to the diagnosis of congenital myopathies." Neuromuscular disorders : NMD vol. 24,2 (2014): 97-116. doi:10.1016/j.nmd.2013.11.003
[3] Tubridy, N et al. "Congenital myopathies and congenital muscular dystrophies." Current opinion in neurology vol. 14,5 (2001): 575-82. doi:10.1097/00019052-200110000-00005
[4] Khadilkar SV, Singh RK. Limb girdle muscular dystrophies in India. Neurol India. 2008 Jul-Sep;56(3):281-8. doi: 10.4103/0028-3886.43446. PMID: 18974554.
[5] Khadilkar, Satish V.; Faldu, Hinaben Dayalal; Patil, Sarika Bapuso; Singh, Rakesh. Limb-girdle Muscular Dystrophies in India: A Review. Annals of Indian Academy of Neurology 20(2):p 87-95, Apr–Jun 2017. | DOI: 10.4103/aian.AIAN_81_17
[6] Kathryn N. North , Ching H. Wang, Nigel Clarke, Heinz Jungbluth , Mariz Vainzof, James J. Dowling, Kimberly Amburgey, Susana Quijano-Roy, Alan H. Beggs , Caroline Sewry, Nigel G. Laing, Carsten G. Bo¨nnemann, Members of the International Standard of Care Committee for Congenital Myopathies. Approach to the diagnosis of congenital myopathies. Neuromuscular Disorders 24 (2014) 97–116. https://doi.org/10.1016/j.nmd.2013.11.003