ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 09 | September - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL AND MOLECULAR SPECTRUM OF PEDIATRIC DYSTROPHINOPATHIES: A CASE SERIES FROM SOUTH INDIA

Neuro Science

Swetha Rampally MD DM, Department of Pediatric Neurology, SparkKids Children's Hospitals, Kurnool
Naveen Reddy G MD DrNB, Department of Pediatric Critical Care, SparkKids Children's Hospitals, Kurnool

ABSTRACT

Background: Dystrophinopathies comprise a spectrum of X-linked muscle disorders caused by pathogenic variants in the DMD gene, ranging from the severe Duchenne muscular dystrophy (DMD) phenotype to the milder Becker muscular dystrophy (BMD) phenotype. Although progressive proximal weakness, Gowers' sign, calf pseudohypertrophy, and marked creatine kinase (CK) elevation are characteristic, atypical presentations may complicate clinical recognition. Advances in next-generation sequencing (NGS) and copy-number variant (CNV) analysis have expanded molecular diagnosis in both typical and non-representative phenotypes. **Objectives:** To characterize the clinical and molecular spectrum of children evaluated for suspected dystrophinopathy at a tertiary pediatric neurology center in South India and to examine the relationship between phenotype and genetic findings. **Methods:** We retrospectively reviewed eight children referred for evaluation of suspected inherited muscular disorders. Demographic characteristics, age at onset, presenting manifestations, neurological findings, CK levels, and molecular findings were analyzed. Genetic testing was performed using NGS/whole-exome sequencing with CNV analysis, according to the testing platform used by the referring laboratory. **Results:** Eight children, aged 6 months to 12 years, were evaluated. Five boys had pathogenic/likely pathogenic hemizygous DMD deletions involving exons 45–52, consistent with dystrophinopathy. Clinical manifestations included difficulty running, progressive proximal weakness, waddling gait, Gowers' sign, calf hypertrophy, and ankle contractures. CK levels reached 15,560 IU/L and 16,630 IU/L in two patients, while one genetically confirmed case had a CK level of 636 IU/L. One female child with proximal weakness and Gowers' sign had a homozygous SGCB c.544A>C (p.Thr182Pro) variant. Two infants with hypotonia and developmental delay had variants of uncertain significance involving COL6A2 and FKBP14/DNAJB6, respectively. **Conclusion:** This case series demonstrates substantial clinical and molecular heterogeneity among children presenting with suspected dystrophinopathy. DMD exon deletions predominated among confirmed cases and clustered within the deletion-rich region. Broad molecular testing also identified alternative neuromuscular diagnoses or unresolved findings in clinically overlapping cases.

KEYWORDS

dystrophinopathy; Duchenne muscular dystrophy; Becker muscular dystrophy; DMD; genotype-phenotype correlation; next-generation sequencing; copy-number variation; pediatric neurology.

INTRODUCTION

Dystrophinopathies are X-linked muscular disorders caused by pathogenic variants in the DMD gene and encompass a broad clinical continuum, principally represented by Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). The phenotypic distinction between these disorders is traditionally related to the amount and functionality of dystrophin, although genotype-phenotype relationships are not absolute.[8,9]

DMD typically manifests during early childhood with progressive proximal muscle weakness, difficulty running or climbing stairs, waddling gait, Gowers' sign, calf pseudohypertrophy, and markedly elevated serum CK levels. BMD generally has a later onset and a more slowly progressive course. Genetic studies have demonstrated considerable heterogeneity in DMD mutations, with large exon deletions representing a major proportion of pathogenic variants.[3,8,9]

The phenotypic spectrum extends beyond skeletal muscle. Dystrophin is expressed in the central nervous system, and cognitive, behavioral, emotional, and social difficulties are increasingly recognized components of dystrophinopathy.[1,2,4]

A further diagnostic challenge is the occurrence of atypical or non-representative phenotypes. Dystrophinopathy may mimic metabolic or other inherited myopathies, while broad NGS-based testing can identify pathogenic variants in patients whose presentations do not fit the classical phenotype.[3,5,6]

Female patients can rarely manifest clinically significant dystrophinopathy, including through skewed X-chromosome inactivation or other mechanisms. Symptomatic girls may present with pro-ximal weakness, calf hypertrophy, gait abnormalities, or elevated CK.[7]

We describe a series of eight children evaluated for suspected dystrophinopathy, emphasizing integration of phenotype and genotype and the diagnostic insights obtained through molecular testing.

METHODS

This retrospective descriptive case series included eight children evaluated in a tertiary pediatric neurology practice in South India for suspected inherited neuromuscular disease.

Clinical information was obtained from available medical records and included age, sex, age at symptom recognition/onset, presenting symptoms, pattern of weakness, Gowers' sign, gait abnormalities, calf hypertrophy, contractures, hypotonia, developmental delay, CK levels, transaminase abnormalities, electrophysiological findings where available, and relevant family history.

Genetic testing was performed by whole-exome sequencing or NGS-based testing with CNV analysis, depending on the laboratory and test ordered. Variants were interpreted according to the classification reported by the respective laboratory. Variants reported as variants of uncertain significance (VUS) were not considered definitive molecular diagnoses.

RESULTS

Eight children, seven males and one female, aged 6 months to 12 years, were evaluated. Five boys had pathogenic/likely pathogenic hemizygous DMD deletions. Three additional patients had alternative or unresolved molecular findings involving SGCB, COL6A2, and FKBP14/DNAJB6.

Among the five DMD-related cases, the principal manifestations were progressive proximal weakness, difficulty running or walking, waddling gait, Gowers' sign, calf hypertrophy, and ankle contractures. One patient had speech delay in association with motor difficulties. The two infants with VUS findings had predominantly hypotonia, developmental delay, and feeding/swallowing difficulties.

CK values varied considerably. Documented values included 636 IU/L, 15,560 IU/L, and 16,630 IU/L. Transaminase elevations were present in some patients.

Table 1. Clinical and Molecular Characteristics of the Eight Patients

Case	Age/ Sex	Key phenotype	CK (IU/L)	Molecular finding	Classi-fication
1	10 y/M	Difficulty running; proximal weakness; ankle contractures	Mild elevation	DMD exons 46–47 deletion	Likely patho-genic
2	8 y/M	Speech delay; gait difficulty; calf swelling	636	DMD exons 45–50 deletion	Likely patho-genic
3	12 y/M	Progressive proxi-mal weakness; calf hypertrophy	Elevated	DMD exons 46–52 deletion	Likely patho-genic

4	7 y/M	Proximal > distal weakness; Gowers' sign	15,560	DMD exons 48–52 deletion	Pathogenic
5	10 y/M	Progressive weakness; waddling gait; Gowers' sign	16,630	DMD exon 45-region deletion	Pathogenic
6	10 y/F	Proximal weakness; Gowers' sign	Elevated	SGCB c.544A>C (p.Thr182Pro), homozygous	Likely pathogenic
7	10 mo/M	Hypotonia; developmental delay	Not available	COL6A2 c.2809C>T (p.Arg937Trp), heterozygous	VUS
8	6 m o/M	Hypotonia; flaccidity; swallowing difficulty	Not available	FKBP14 c.349G>T (p.Gly117Cys), homozygous; DNAJB6 VUS	VUS

Genotypic Spectrum

Five patients had hemizygous DMD exon deletions involving the exon 45–52 region. The deletion patterns were exons 46–47, 45–50, 46–52, 48–52, and an exon 45-region deletion. All were classified by the reporting laboratories as pathogenic or likely pathogenic CNVs.

The remaining molecular findings included a homozygous SGCB missense variant associated with limb-girdle muscular dystrophy and VUS findings involving COL6A2 and FKBP14/DNAJB6. The latter were not considered definitive diagnoses.

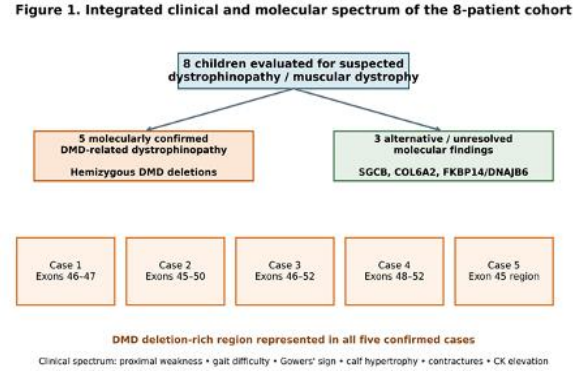

Figure 1. Integrated clinical and molecular spectrum of the eight-patient cohort.

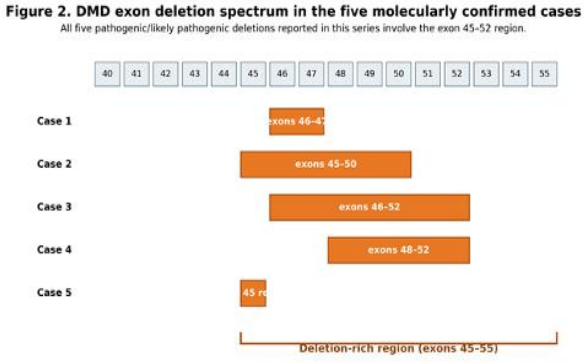

Figure 2. DMD exon deletion spectrum in the five molecularly confirmed cases.

DISCUSSION

The principal finding of this series is the convergence of a recognizable clinical phenotype with substantial molecular heterogeneity among children evaluated for suspected dystrophinopathy.

Five of eight children had molecularly confirmed DMD-related dystrophinopathy, all with large hemizygous deletions involving the exon 45–52 region. Large deletions are a major molecular mechanism in dystrophinopathy, and CNV analysis remains important for their detection.[3,9]

The clinical phenotype of the five confirmed cases was predominantly characterized by proximal weakness, gait difficulty, Gowers' sign, calf hypertrophy, and elevated CK, consistent with the classical DMD/BMD spectrum.[8,9]

CK concentration varied considerably. One genetically confirmed case had a CK level of only 636 IU/L, whereas two had levels above 15,000 IU/L. This reinforces the importance of interpreting CK in the context of the clinical phenotype rather than using a single threshold to exclude dystrophinopathy.

Atypical presentations can mimic metabolic myopathies and other inherited muscular disorders, creating a diagnostic challenge. Conversely, our series demonstrates that a dystrophinopathy-like phenotype does not necessarily imply a DMD variant. Broad molecular testing identified an SGCB-related muscular dystrophy and unresolved VUS findings in other patients.[3,5,6]

The symptomatic female patient is also notable. Female dystrophinopathy is uncommon but well described, and skewed X-chromosome inactivation and other mechanisms can result in clinically significant disease. In the present series, however, the female patient had an SGCB variant rather than a DMD variant, reinforcing the value of comprehensive genetic evaluation in girls with muscular dystrophy phenotypes.[7]

Dystrophinopathy also has an important neurodevelopmental dimension. Dystrophin expression in the brain has prompted increasing interest in cognitive, behavioral, emotional, and social phenotypes. BIND and D-BRAIN studies have specifically investigated relationships between genotype and neurobehavioral phenotype, emphasizing that assessment of dystrophinopathy should extend beyond motor function.[1,2,4]

The practical implication is that clinical recognition and molecular confirmation should be viewed as complementary. A child with proximal weakness, Gowers' sign, calf hypertrophy, and elevated CK warrants evaluation for dystrophinopathy, but a broad neuromuscular testing strategy is particularly valuable when the phenotype is atypical or the initial DMD evaluation is unrevealing.

Strengths

- Integration of clinical phenotype and molecular findings.
- Representation of both classical and atypical neuromuscular presentations.
- Identification of a consistent DMD exon deletion pattern among confirmed cases.
- Recognition of clinically important phenocopies and VUS in a real-world pediatric neuromuscular cohort.
- Addition of regional data from a South Indian tertiary pediatric neurology practice.

LIMITATIONS

The study is limited by its small sample size, retrospective design, and single-center clinical setting. Longitudinal functional, cardiac, respiratory, and formal neuropsychological data were not uniformly available. Muscle biopsy and dystrophin immuno histochemistry/Western blot were not performed in all patients. The study cannot establish population-level frequencies of individual DMD deletions. Finally, VUS findings cannot be considered definitive molecular diagnoses without additional evidence.

Future directions

Larger multicenter Indian cohorts with standardized motor, cardiac, respiratory, cognitive, and behavioral assessments are needed. Future studies should incorporate segregation studies for uncertain variants, confirmatory CNV testing where appropriate, and longitudinal genotype-specific outcome assessment.

CONCLUSION

This case series demonstrates a broad clinical and molecular spectrum among children presenting with suspected dystrophinopathy. Five of eight children had pathogenic/likely pathogenic DMD deletions, predominantly involving the exon 45–52 region, while three had alternative or unresolved molecular findings. The findings emphasize that classical clinical recognition remains valuable, but comprehensive molecular testing is essential when phenotypes overlap. Integrating phenotype, genotype, and cautious variant interpretation is central to accurate diagnosis, counseling, prognostication, and precision-based management.

REFERENCES

1. Colvin MK, Truba N, Sorensen S, Henricson E, Kinnett K. Dystrophinopathy and the brain: a Parent Project Muscular Dystrophy meeting report November 11-12, 2021, New York City, NY. Neuromuscul Disord. 2022;32(11):935-944.

2. Brain INvolvement in Dystrophinopathies (BIND): Deep Functional Phenotyping of Duchenne Muscular Dystrophy and Becker Muscular Dystrophy Patients (WP5 and WP6) Part 2: a Neurobehavioural and MRI Study. ClinicalTrials.gov identifier NCT04668716.
3. Wang L, Jacoby E, Bell S, Stubbs D, Mayo P, Vilt M, et al. P681: Molecular diagnosis of DMD-related dystrophinopathies in patients with non-representative phenotypes by using a broad neuromuscular next generation sequencing (NGS) panel. Genet Med Open. 2025;3:103050.
4. Social Cognition in Dystrophinopathies and Neurodevelopmental Disorders. Behavioural and Psychophysiological Measures. ClinicalTrials.gov identifier NCT06874166. 2025.
5. Liewluck T, Tian X, Wong LJ, Pestronk A. Dystrophinopathy mimicking metabolic myopathies. Neuromuscul Disord. 2015;25(8):653-657.
6. McMillan HJ, Darras BT. Atypical dystrophinopathy phenotypes. In: Swaiman's Pediatric Neurology. 2026.
7. Seemann N, Selby K, McAdam L, Biggar D, Kolski H, Goobie S, et al. Symptomatic dystrophinopathies in female children. Neuromuscul Disord. 2011;21(3):172-177.
8. Rae-Grant A, van Zuuren EJ, Valentine S. Duchenne and Becker muscular dystrophies. DynaMed. 2025.
9. Na SJ, Kim WJ, Kim SM, Lee KO, Yoon B, Choi YC. Clinical, immunohistochemical, Western blot, and genetic analysis in dystrophinopathy. J Clin Neurosci. 2013;20(8): 1099-1105.
10. Defining Outcome Measures for Behavioural and Emotional Problems in Dystrophinopathies (D-BRAIN). ClinicalTrials.gov identifier NCT06581887. 2024.