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Original Research Paper

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BEYOND HYPOTONIA: THE DIVERSE PHENOTYPIC SPECTRUM OF CONGENITAL MYOPATHIES IN INFANCY A CASE SERIES

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ABSTRACT

Background: Congenital myopathies are a group of inherited neuromuscular disorders characterized by early-onset muscle weakness, hypotonia, and distinctive structural abnormalities of skeletal muscle fibers. Although traditionally classified based on histopathological findings, clinical phenotypes may vary widely and often overlap among subtypes. **Objective:** To describe the clinical and phenotypic spectrum of children presenting with congenital myopathy in a tertiary pediatric neurology center. **Methods:** This retrospective case series included six children presenting with early-onset hypotonia and motor developmental delay. Clinical characteristics, neurological examination findings, neuroimaging results, and associated systemic features were analyzed to characterize the phenotypic spectrum. **Results:** Six children with suspected congenital myopathy were evaluated. The median age at presentation was 10 months. All patients presented with generalized hypotonia and delayed motor milestones. Additional clinical manifestations included facial weakness, external ophthalmoplegia, orthopedic abnormalities such as clubfoot, dysmorphic facial features, and respiratory involvement. Neuroimaging findings were largely nonspecific. The phenotypic spectrum ranged from mild motor delay to severe hypotonia with inability to achieve head control. **Conclusion:** Congenital myopathies demonstrate considerable clinical heterogeneity in infancy. Early recognition of characteristic phenotypic features, including hypotonia, facial weakness, and skeletal abnormalities, is essential for prompt diagnosis and appropriate genetic evaluation.

KEYWORDS : Congenital Myopathy, Infantile Hypotonia, Phenotypic Spectrum, Neuromuscular Disorders

INTRODUCTION

Congenital myopathies represent a heterogeneous group of inherited neuromuscular disorders characterized by early-onset muscle weakness and structural abnormalities of skeletal muscle fibers[1,2]. These disorders were historically classified based on characteristic histopathological features observed on muscle biopsy, including nemaline rods, central nuclei, and core lesions[2].

Over the past several decades, advances in molecular genetics have significantly expanded the understanding of congenital myopathies, revealing a broad spectrum of genetic etiologies and clinical phenotypes[3]. Despite these advances, the clinical presentation often remains the initial clue to diagnosis, particularly in infants presenting with hypotonia and delayed motor milestones[6].

The phenotypic manifestations of congenital myopathies are highly variable and may include generalized hypotonia, muscle weakness, facial weakness, feeding difficulties, respiratory involvement, and skeletal abnormalities such as scoliosis or clubfoot[6]. In some cases, distinctive craniofacial features or ophthalmoplegia may provide additional diagnostic clues[7].

Several studies have highlighted the wide clinical variability of congenital myopathies, with severity ranging from mild motor delay to severe neonatal hypotonia requiring respiratory support[8,9]. Early identification of characteristic clinical patterns is essential for guiding diagnostic evaluation and facilitating timely genetic testing.

In this study, we describe the phenotypic spectrum of congenital myopathies observed in a series of six infants evaluated at a tertiary pediatric neurology center.

METHODS

Study Design

This retrospective case series was conducted at a tertiary pediatric neurology center. Medical records of children evaluated for suspected congenital myopathy between 2023 and 2026 were reviewed.

Inclusion Criteria

Children were included if they had:

- Early-onset hypotonia
- Motor developmental delay
- Clinical suspicion of congenital myopathy

Data Collection

Clinical data were extracted from patient records, including:

- Age at presentation
- Sex
- Consanguinity
- Clinical symptoms
- Neurological examination findings
- Skeletal and dysmorphic features
- Neuroimaging findings

Ethical Considerations

Patient identifiers were removed to maintain confidentiality, and the study adhered to institutional ethical guidelines.

RESULTS

Demographic Characteristics

Six children with suspected congenital myopathy were included in the study. The median age at presentation was 10 months (range 8–12 months). Four patients were male and two were female. Consanguinity was reported in four families.

Clinical Presentation

All patients presented with generalized hypotonia and delayed motor milestones.

Additional Clinical Features Included:

- External ophthalmoplegia and facial weakness in one patient
- Bilateral clubfoot in two patients
- Dysmorphic facial features including down-slanting palpebral fissures in one patient
- Respiratory involvement in one patient
- Positive family history of neuromuscular disease in one patient

The severity of motor impairment varied across the cohort. One patient exhibited severe hypotonia with inability to achieve head control, while others demonstrated delayed acquisition of gross motor milestones.

Neurological Examination

Neurological examination revealed generalized hypotonia in all patients, with reduced muscle tone predominantly affecting the axial musculature. Muscle weakness was most evident in proximal muscle groups. Deep tendon reflexes were reduced in several patients but preserved in others.

Facial involvement, including mask-like facies and facial weakness, was observed in one patient. Ophthalmoplegia was also noted in the same case.

Skeletal and Dysmorphic Features

Orthopedic abnormalities were present in two patients in the form of bilateral clubfoot. Craniofacial dysmorphism including bitemporal hollowing and down-slanting eyes was observed in some patients.

Neuroimaging Findings

Magnetic resonance imaging of the brain was performed in most patients and was largely nonspecific. Findings included mild ventricular asymmetry and subtle white matter abnormalities in some cases, while other scans were normal.

DISCUSSION

Congenital myopathies are characterized by significant clinical heterogeneity, which often complicates early diagnosis. Infants typically present with hypotonia and delayed motor milestones, making clinical recognition essential in guiding further diagnostic evaluation[10].

In the present series, generalized hypotonia and delayed motor development were universal features, consistent with previous studies describing these findings as hallmark manifestations of congenital myopathies[6]. Facial weakness and ophthalmoplegia, although less common, may provide important diagnostic clues and have been reported in several congenital myopathy subtypes[7].

Orthopedic abnormalities such as clubfoot were observed in two patients in our cohort. Skeletal deformities have been described in congenital myopathies and may result from reduced fetal or early postnatal muscle activity[6].

The variability in clinical severity observed in this study reflects the broad phenotypic spectrum of congenital myopathies. Some patients exhibited relatively mild motor delay, while others demonstrated severe hypotonia and profound motor impairment. Similar phenotypic variability has been reported in previous clinical series of congenital myopathy patients[10].

Neuroimaging findings were largely nonspecific in our cohort. Brain MRI is typically normal in congenital myopathies, although mild white matter changes may occasionally be observed[6].

Overall, the findings of this study highlight the importance of careful clinical evaluation in infants presenting with hypotonia. Recognition of characteristic phenotypic features may facilitate early diagnosis and prompt genetic evaluation.

CONCLUSION

Congenital myopathies demonstrate a wide range of clinical manifestations in infancy. Generalized hypotonia and delayed motor milestones remain the most common presenting features. Additional findings such as facial weakness, ophthalmoplegia, and skeletal abnormalities may provide important diagnostic clues. Early recognition of these phenotypic patterns is crucial for guiding further diagnostic evaluation and management.

Key Messages

What is known

- Congenital myopathies are a heterogeneous group of neuromuscular disorders presenting with infantile hypotonia.

What this Study Adds

- This case series highlights the broad phenotypic spectrum of congenital myopathies in infancy.

Clinical Implications

- Early recognition of clinical features such as hypotonia, facial weakness, and skeletal abnormalities can facilitate timely diagnosis.

Table. Structured Phenotypic Comparison of Patients with Congenital Myopathy

Clinical Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at presentation	12 mo	8 mo	12 mo	11 mo	10 mo	Infant
Sex	Male	Female	Female	Male	Male	Not specified
Consanguinity	Yes	Yes	No	No	Yes	Yes
Hypotonia	Yes	Yes	Yes	Yes	Yes	Yes
Motor developmental delay	Yes	Yes	Yes	Yes	Yes	Yes
Facial weakness / mask-like facies	Yes	No	No	No	No	No
Ophthalmoplegia	Yes	No	No	No	No	No
Dysmorphic facial features	Yes	Yes	Yes	No	No	No
Clubfoot / orthopedic abnormality	Yes	Yes	No	No	No	No
Respiratory involvement	No	No	No	No	No	Yes
Family history	No	No	No	No	Yes	No
Deep tendon reflexes	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
Neuroimaging abnormalities	Mild ventricular asymmetry	Caudate T2 hyperintensity	Thin white matter	Normal	Not available	Not available

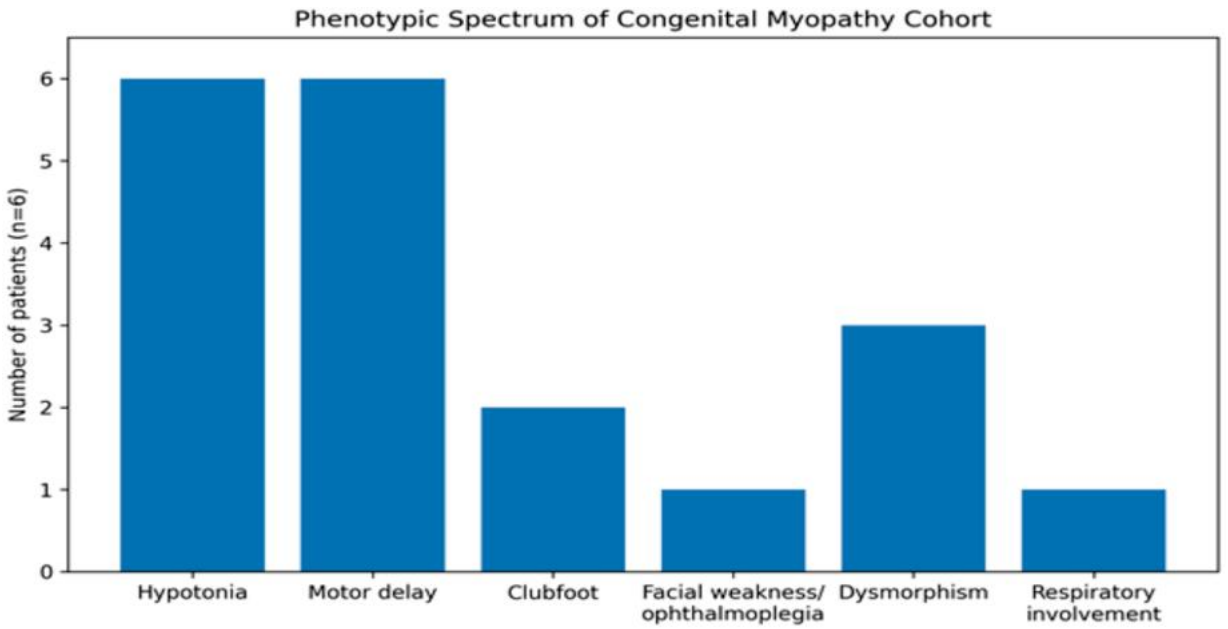
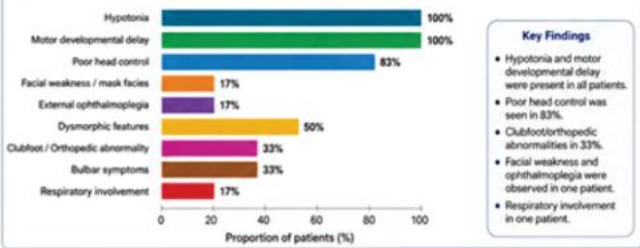


Table 1. Structured Phenotypic Comparison of the 6 Patients with Congenital Myopathy

Clinical Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at presentation	12 months	8 months	12 months	11 months	10 months	Infant
Sex	Male	Female	Female	Male	Male	Not specified
Consanguinity	Yes	Yes	No	No	Yes	Yes
Mode of onset	Congenital	Congenital	Congenital	Congenital	Congenital	Congenital
Pregnancy / Perinatal history	Term, uneventful	Term, uneventful	Term, uneventful	Term, uneventful	Term, uneventful	Term, uneventful
Hypotonia	Yes	Yes	Yes	Yes	Yes	Yes
Motor developmental delay	Yes	Yes	Yes	Yes	Yes	Yes
Poor head control	No (partial control)	Yes	Yes	Yes (none)	Yes	Yes
Ability to sit	Not achieved	Not achieved	Not achieved	Not achieved	Not achieved	Not achieved
Ability to stand / walk	No	No	No	No	No	No
Facial weakness / mask-like facies	Yes	No	No	No	No	No
External ophthalmoplegia	Yes	No	No	No	No	No
Dysmorphic features	Bitemporal hollowing, mask-like facies	White forelock	Down slanting eyes	No	No	No
Clubfoot / Orthopedic abnormality	Bilateral clubfoot	Bilateral clubfoot	No	No	No	No
Contractures / Joint laxity	No	No	No	No	No	No
Respiratory involvement	No	No	No	No	No	Yes (distress episodes)
Bulbar symptoms (feeding difficulty)	Mild	No	No	Yes (poor suck)	No	Yes
Deep tendon reflexes	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
CK level	Normal	Normal	Normal	Normal	Normal	Normal
Neuroimaging (MRI brain)	Mild ventricular asymmetry, simplified gyral pattern	T2 hyperintensity in bilateral caudate nuclei	Thin white matter	Normal	Not done	Not done
Family history	No	No	No	No	Yes (similar illness)	No

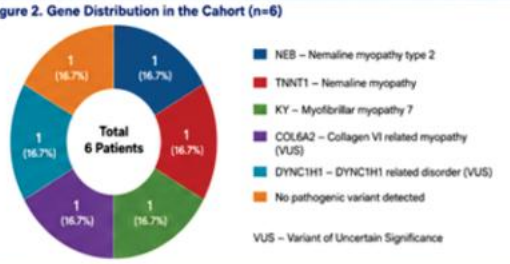
Figure 1. Phenotypic Spectrum of Congenital Myopathies in the Study Cohort (n=6)



Key Findings

- Hypotonia and motor developmental delay were present in all patients.
- Poor head control was seen in 83%.
- Clubfoot/orthopedic abnormalities in 33%.
- Facial weakness and ophthalmoplegia were observed in one patient.
- Respiratory involvement in one patient.

Figure 2. Gene Distribution in the Cohort (n=6)



Discussion: Comparison of Our Cases with Global Literature

- Our cohort reflects the wide clinical heterogeneity reported in congenital myopathies. Consistent with previous large studies, hypotonia and motor developmental delay were universal findings [4–6].
- Nemaline myopathy was the most frequent molecular finding (*NEB* and *TNNT1*), in keeping with global data where these genes are among the most common causes of congenital nemaline myopathy [1–6]. NEB-related disease [6,10]. NEB-related disease shows a broad severity spectrum from severe neonatal weakness to milder childhood onset [8–10]. Our patient on heterozygous similar to reports in literature [5–7].
- *TNNT1*-related nemaline myopathy is typically associated with severe infantile onset, central hypotonia and delayed milestone [3,5,6] variable [1,7–9].
- *KY*-related myopathy (myofibrillar myopathy 7) is rare and characterized by early weakness, contractures and skeletal abnormalities [3,7]. motor delay and bilateral clubfoot, aligning with reported phenotype [3,7].
- *COL6A2*-related disorders (Bethlem myopathy / Ullrich congential muscular dystrophy) show variable onset from congenital hypotonia to later childhood weakness with joint contractures [3,4]. Our patient had a heterozygous VUS; clinical overlap exists, but segregation and functional validation are needed.
- *DYNC1H1* variants are increasingly recognized in neuromuscular disorders including congenital hypotonia and respiratory involvement [7]. Our patient had hypotonia with respiratory distress episodes, compatible with this spectrum.
- One patient remained genetically unresolved despite extensive testing, which is in line with previously reported diagnostic yield (40–60%) in congenital myopathies [9,10]. This highlights the limitations of current sequencing and the need for further studies including CNV analysis, RNA studies or advanced genomic techniques.

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