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CASE REPORT

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Diagnostic Reappraisal after 12-Year Follow-up of Pediatric Myopathy with Heterozygous *NEB* Variants and Dystrophy-Like Progression

Afërdita Tako[1], Mirela Tabaku[2*], Aida Bushati[3], Rovena Aliaj[1], Armand Shehu[1], Sindi Dizdari[1], Paskal Cullufi[3]

[1]*Department of Pediatrics, Mother Teresa University Hospital Center, Tirana, Albania*
[2]*Department of Pediatrics, Genetics Service, University of Medicine Tirana, Tirana, Albania*
[3]*Department of Pediatrics, University of Medicine Tirana, Tirana, Albania*

Abstract

Background: Mutations in the *NEB* gene are the most frequent genetic cause of autosomal recessive nemaline myopathy, a clinically heterogeneous congenital myopathy.
In pediatric myopathy, longitudinal observation is essential because the evolving phenotype may challenge an initially plausible molecular interpretation and reveal features requiring diagnostic reappraisal.
Case presentation: This report describes a 12-year clinical-genetic trajectory in a child with congenital-onset myopathy, persistent hyperCKemia, two heterozygous *NEB* variants, and later dystrophy-like progression. Clinical exome sequencing performed at 5 years of age identified two heterozygous *NEB* variants: the canonical splice-site variant c.10872+1G>C and the missense variant c.11333T>C (p.Ile3778Thr). The patient achieved independent ambulation at 20 months but later developed progressive weakness, Gowers' sign, scapular winging, distal muscle wasting, and progressive functional decline, ultimately losing independent ambulation at 12 years. Cardiac and respiratory assessments remained normal during follow-up.
Conclusions: This report describes a 12-year clinical-genetic trajectory in a child with congenital-onset myopathy, persistent hyperCKemia, two heterozygous *NEB* variants of unresolved phase, and later dystrophy-like progression. The longitudinal course highlights the importance of cautious interpretation of exome findings and supports ongoing diagnostic reappraisal when evolving features broaden the neuromuscular differential diagnosis. (**International Journal of Biomedicine. 2026;16(3):401-405.**)

Keywords: *NEB* • nemaline myopathy • pediatric myopathy • hyperCKemia • longitudinal follow-up • diagnostic reappraisal

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Introduction

Nemaline myopathy (NM) is a genetically heterogeneous congenital myopathy characterized by skeletal muscle weakness, hypotonia, and nemaline rods on muscle histopathology. Among the currently recognized disease genes, *NEB*, which encodes nebulin, is one of the most frequent causes of autosomal recessive NM. Nebulin is a large thin-filament protein involved in sarcomeric organization, thin-filament length regulation, and force generation, and *NEB*-related disease spans a broad clinical spectrum ranging from severe neonatal presentations to milder childhood phenotypes compatible with prolonged ambulation.[1-4]

The increasing use of next-generation sequencing has improved the diagnostic work-up of pediatric neuromuscular disorders. However, the clinical value of a molecular finding is maximized when it is interpreted together with the longitudinal phenotype. This is particularly relevant when a child with congenital-onset motor impairment later develops persistent hyperCKemia, calf pseudohypertrophy, Gowers' sign, scapular winging, and progressive loss of ambulation, a pattern that can overlap with muscular dystrophy.[3-6]

This report describes the 12-year longitudinal course of a child with two heterozygous *NEB* variants whose phenotype evolved from congenital-onset myopathy toward dystrophy-like progression with persistent hyperCKemia and loss of

ambulation. Rather than presenting the findings as definitive proof of *NEB* causality, the case illustrates how long-term clinical evolution may challenge an initially plausible molecular interpretation and support diagnostic reappraisal when the phenotype broadens.

Case Presentation

The patient was a boy born at term after an uncomplicated pregnancy and spontaneous vaginal delivery, with normal neonatal adaptation and no known family history of neuromuscular disease. Motor delay became evident from infancy. Head control was achieved at 4 months, independent sitting at 8 months, supported walking at 15 months, and independent ambulation at 20 months, indicating early motor impairment despite eventual acquisition of walking.

Initial neurological evaluation showed generalized hypotonia, absent deep tendon reflexes, paraspinal muscle atrophy, and mild gastrocnemius pseudohypertrophy. Cranial nerve function was preserved, and no persistent bulbar dysfunction was clearly documented during follow-up. Electromyography demonstrated a myopathic pattern.

Serial biochemical investigations provided consistent evidence of chronic muscle involvement. At the initial evaluation, serum AST was 100 U/L, ALT was 80 U/L, CK was 1500 U/L, and LDH was 800 U/L. These abnormalities persisted during follow-up; representative later values included AST 80 U/L, ALT 70 U/L, CK 1000 U/L, and LDH 700 U/L. Overall, CK remained approximately within the range of 1000-1500 U/L across the available longitudinal data.

Although the patient achieved independent ambulation, progressive motor deterioration became evident during childhood. He developed Gowers' sign, scapular winging, distal muscle wasting, and worsening weakness with increasing functional limitation. Within the available documentation, no clear contractures, scoliosis, or persistent facial or bulbar involvement were consistently recorded. Serial clinical cardiopulmonary evaluations remained reassuring, with no documented evidence of cardiac involvement or overt respiratory compromise. Independent ambulation was ultimately lost at age 12.

Clinical exome sequencing performed at 5 years of age identified two heterozygous *NEB* variants: c.10872+1G>C, a canonical splice-site variant, and c.11333T>C (p.Ile3778Thr), a missense variant. The diagnostic laboratory considered the findings supportive of possible NEB-associated disease and recommended parental testing to determine whether the variants were in trans. Parental segregation analysis was not performed; therefore, the phase of the variants remains unresolved. In addition, dedicated dystrophinopathy testing, including DMD deletion/duplication analysis, was not documented in the available initial diagnostic workup.

Differential diagnosis

At presentation, the combination of infantile hypotonia, delayed motor milestones, absent deep tendon reflexes, and a myopathic electromyographic pattern supported congenital myopathy. Over time, persistent CK elevation of approximately 1000-1500 U/L, mild calf pseudohypertrophy, Gowers' sign, progressive weakness, and childhood loss of ambulation broadened the clinical differential toward dystrophinopathy and other inherited muscular dystrophies.

The identification of two heterozygous NEB variants made NEB-associated disease a plausible molecular consideration for the early congenital-onset phenotype. However, because the phase was not established and the subsequent clinical course showed dystrophy-like progression, the case is best interpreted as a clinically informative overlap between features of congenital myopathy and a progressive dystrophic phenotype. This framing highlights that longitudinal follow-up can refine diagnosis, redirect differential thinking, and identify patients who may require additional evaluation beyond the initial exome result. The longitudinal clinical course is summarized in Table 1.

Table 1.

Twelve-year clinical and diagnostic timeline: Developmental, biochemical, molecular, and functional milestones documented during follow-up.

Age/period	Key finding	Clinical meaning
Infancy	Hypotonia; delayed milestones	Congenital-onset neuromuscular disease
20 months	Independent ambulation achieved	Early gain despite motor delay
Childhood	CK approximately 1000-1500 U/L; Gowers' sign; scapular winging	Progressive skeletal-muscle involvement
5 years	Two heterozygous NEB variants identified	Plausible NEB-related molecular consideration; allelic phase unresolved
12 years	Loss of independent ambulation	Major marker of dystrophy-like progression

Discussion

This case is characterized by a long clinical course in which congenital-onset features were followed by substantial dystrophy-like progression over 12 years. Infantile hypotonia, delayed motor milestones, absent reflexes, and a myopathic electromyographic pattern supported a congenital myopathy presentation and could fit within the broad *NEB*-associated disease spectrum. The later emergence of persistent marked hyperCKemia, Gowers' sign, scapular winging, distal wasting, and loss of independent ambulation shifted the interpretation toward a more complex clinicogenetic picture.

Published studies of *NEB*-associated NM emphasize broad phenotypic heterogeneity and variable motor, bulbar, respiratory, and skeletal muscle involvement. [1-4] The present case spans a long observation window from early motor delay to later functional decline, providing a clearer view of phenotypic evolution over time (Figure 1). This longitudinal dimension is clinically relevant: a child who initially achieves independent walking may still develop a progressive course that changes the diagnostic interpretation, surveillance priorities, and management questions.

Figure 1. *Longitudinal clinic-genetic timeline summarizing the major developmental, molecular, and functional milestones during the 12-year follow-up.*

The molecular findings are clinically relevant but should be interpreted cautiously. The canonical splice-site variant c.10872+1G>C represents the stronger molecular finding, whereas p.(Ile3778Thr) requires contextual interpretation in relation to the patient's phenotype and available variant literature. [7,10] Together, the two identified *NEB* variants provide a plausible but not definitive molecular explanation, as parental segregation analysis was not performed, and the allelic phase remains unresolved. Therefore, a confirmed biallelic *NEB*-related disorder cannot be established based on the available data. Key clinical and molecular features informing the diagnostic interpretation are summarized in Table 2.

Phenotype evolution remains central in pediatric neuromuscular disease. In a male patient with persistent hyperCKemia, calf pseudohypertrophy, progressive weakness, Gowers' sign, and childhood loss of ambulation, dystrophinopathy and other muscular dystrophies remain important clinical considerations. [8,9] In the present case, longitudinal follow-up revealed a dystrophy-like trajectory despite early features and molecular findings that initially pointed toward congenital myopathy.

This case underscores a key diagnostic principle in pediatric neuromuscular disorders: early genotype-phenotype correlation may remain provisional, particularly when longitudinal clinical evolution introduces atypical features for the initially suspected condition. In such scenarios, maintaining a dynamic diagnostic framework and reconsidering alternative etiologies is essential. Table 3 summarizes selected recent literature relevant to pediatric and *NEB*-associated nemaline myopathy, providing context for the longitudinal features observed in the present patient.

Table 2.

Clinical and molecular features informing diagnosis: Summary of the principal findings supporting possible NEB involvement and features broadening the neuromuscular differential diagnosis.

Domain	Features supporting possible NEB involvement	Features broadening the differential diagnosis
Early phenotype	Hypotonia, delayed milestones, myopathic EMG	Congenital myopathy presentation
Molecular findings	Two heterozygous NEB variants; one canonical splice-site allele	Missense variant requires contextual interpretation; allelic phase unresolved
Biochemistry	Persistent muscle enzyme elevation	CK, approximately 1000-1500 U/L, broadens the differential toward dystrophic disorders
Motor course	Early congenital myopathy-compatible presentation	Loss of ambulation at 12 years
Cardiorespiratory follow-up	No cardiac/respiratory involvement documented	Predominantly skeletal-muscle course

Table 3.

Selected literature context for interpreting the present longitudinal phenotype.

Study	Clinical context	Motor/CK profile	Interpretive value	Relevance to present case / limitation
Christophers et al., 2023 [2]	Pediatric NM systematic review	Broad heterogeneity	Frames pediatric NM variability	Supports heterogeneity but does not establish causality in an individual case
Amburgey et al., 2021 [9]	Cross-sectional NM study	Disability spectrum	Contrasts with marked decline	Useful comparator for severity, but cross-sectional design limits longitudinal inference
Moreno et al., 2023 [3]	NEB-specific cohort	Variable progression	Key NEB comparator	Relevant NEB cohort, although the present patient lacks a confirmed biallelic phase
Haidong et al., 2024 [10]	Clinicopathologic NM series	Pathology-informed cases	Shows value of orthogonal data	Highlights the limitation created by the absence of a muscle biopsy in the present case
Chalipat et al., 2024 [11]	Pediatric NEB case	Normal CK	Highlights CK contrast	Contrasts with persistent hyperCKemia in the present patient
Present case	12-year follow-up	CK of 1000-1500 U/L; loss of ambulation	Educational diagnostic reappraisal	Longitudinal observation, but causality remains limited by unresolved phase and incomplete dystrophy work-up

Clinical Implications

This case emphasizes that persistent hyperCKemia, Gowers' sign, calf pseudohypertrophy, scapular winging, and loss of ambulation should prompt diagnostic re-evaluation for dystrophinopathy or other muscular dystrophies, even when exome sequencing identifies plausible variants in a congenital myopathy gene. For similar patients, a longitudinal approach that combines repeated functional assessments, updated variant interpretations, and targeted re-evaluations as the phenotype evolves may be particularly informative. This longitudinal perspective may be useful for clinicians evaluating children with overlapping congenital myopathy and muscular dystrophy features.

Diagnostic Limitations

Several methodological constraints should be considered when interpreting this case. Parental segregation analysis was not performed; therefore, the allelic phase remained unresolved. Although clinical exome sequencing was performed, additional orthogonal investigations, including muscle biopsy, muscle MRI, RNA-based analysis, and targeted CNV-sensitive assessment of dystrophinopathy-associated genes, were not available. Therefore, the findings should be interpreted as a longitudinal clinical-genetic observation rather than as definitive proof of *NEB* causality. These limitations do not eliminate the clinical value of the report, but they define its appropriate interpretation.

Conclusion

This report documents a 12-year clinicogenetic follow-up of a child with congenital-onset myopathy, persistent hyperCKemia, two heterozygous *NEB* variants of unresolved phase, and subsequent dystrophy-like progression with loss of ambulation. The case highlights the importance of longitudinal phenotyping and cautious interpretation of molecular findings, particularly when evolving clinical features broaden the differential diagnosis toward muscular dystrophy. Longitudinal multidisciplinary reassessment remains particularly important in such complex neuromuscular presentations.

AI Statement

AI-assisted tools were used solely for language editing and manuscript formatting, based on scientific material provided by the authors.

Ethics Statement

Written informed consent for publication of the clinical details was obtained from the patient's parents/legal guardians. Ethical review and approval were waived because this study represents a retrospective descriptive case report without experimental intervention. The study was conducted in accordance with the Declaration of Helsinki and institutional ethical standards.

Author Contributions

Afërdita Tako contributed to conceptualization, literature review, patient evaluation and clinical follow-up.
Mirela Tabaku contributed to conceptualization, literature review, interpretation of clinical-genetic findings, manuscript drafting, and final manuscript revision.
Aida Bushati, Rovena Aliaj, Armand Shehu, Sindi Dizdari, and Paskal Cullufi contributed to clinical data collection, interpretation, and critical revision of the manuscript.
All authors reviewed and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data supporting the findings of this study are included within the article. Additional information is available from the corresponding author upon reasonable request.

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***Corresponding author:** *Assoc. Prof. Dr. Mirela Tabaku. Department of Pediatrics, Genetics Service, University of Medicine Tirana, Tirana, Albania. E-mail: mtabaku@yahoo.com.*