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Case Report

Severe Neonatal Nemaline Myopathy Associated with NEB Gene Mutation: A Case Report

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Abstract

Introduction: Nemaline myopathy (NM) is among the most common congenital myopathies, typically presenting with non-progressive or slowly progressive generalized muscle weakness. Histologically, NM is characterized by the presence of nemaline bodies-rod-shaped, Z-line-derived structures within skeletal muscle fibers. To date, mutations in at least twelve genes have been implicated in NM, underscoring its considerable molecular heterogeneity. Among these, mutations in NEB and ACTA1 are most frequently identified.

Case Report: We report the case of a 56-day-old female neonate who presented with poor activity and tone at birth, with generalized hypotonia, weak reflexes, a feeble cry, and flexion contractures of both upper limbs. Pooling of secretions suggested possible bulbar involvement. Based on these neurological findings, a neuromuscular disorder was suspected. Whole-exome sequencing (WES) identified a heterozygous, likely pathogenic variant in the NEB gene, consistent with Nemaline Myopathy Type 2 (NEM2), a recessive neuromuscular condition associated with NEB mutations.

Discussion: Nemaline myopathy represents a clinically and genetically heterogeneous group of disorders that can present in the neonatal period with profound hypotonia, respiratory weakness, and feeding difficulties. Muscle biopsy and genetic testing remain key diagnostic tools. Identification of NEB gene variants through WES has significantly improved the ability to confirm the diagnosis and guide family counseling. Although there is currently no definitive cure, early diagnosis allows for timely initiation of supportive care, including respiratory assistance, nutritional management, and physiotherapy.

Conclusion: This case emphasizes the importance of early recognition of clinical signs suggestive of congenital myopathies. Prompt genetic testing facilitates accurate diagnosis, prognosis estimation, and appropriate multidisciplinary management, ultimately improving patient outcomes and aiding family planning through genetic counseling.

Keywords: *Nemaline Myopathy (NM); NEB Gene Mutation; Whole-Exome Sequencing (WES); Nemaline Myopathy Type 2 (NEM2)*

Introduction

Nemaline myopathy (NM) is one of the most common congenital myopathies, with an estimated incidence of 1 in 50,000 live births [1,2]. It encompasses a genetically and clinically heterogeneous group of primary skeletal muscle disorders, characterized histopathologically by nemaline bodies (rods) within muscle fibers. Clinically, NM presents with a spectrum of severity ranging from severe neonatal forms, which may be life-threatening, to milder phenotypes manifesting in childhood or even adulthood [1,4]. The disease typically leads to non-progressive or slowly progressive generalized muscle weakness, although the rate and extent of progression can vary widely between individuals. To date, mutations in at least 12 different genes have been identified as causative, reflecting the complex molecular underpinnings of the condition [1]. We present a case of NM diagnosed in a neonate, emphasizing diagnostic challenges and management considerations.

Case Report

Case discusses a 56-day-old female neonate at the time of writing, who was born to a 40-year-old G2P1L1 woman via emergency LSCS mode of delivery. The baby did not cry at birth and had poor activity at the time of delivery, for which intermittent positive pressure ventilation was initiated, which subsequently improved the vitals and APGAR score. The infant still had persistent respiratory distress, increasing FiO_2 requirements and x-ray changes suggestive of respiratory distress syndrome, for which surfactant was administered. However, clinical improvement was not observed which prompted the initiation of mechanical ventilation. Upon further examination in the NICU, it was found that the baby had poor activity, tone, reflexes, and a weak cry with flexion contractures of bilateral upper limbs. There was pooling of secretions which suggested a possible bulbar involvement. In view of the neurological findings along with neuromuscular evaluation, we considered the possibility of myopathy. Metabolic and other neurological workups were also done to rule out other possibilities.

Family history further revealed second degree consanguinity in the parent's marriage. Tests such as routine blood work, CPK, Ammonia, Lactate, Thyroxine, Blood sugar, NSG, MLPA, MRI brain, amongst others were performed in order to help aid the investigative process.

CPK test results showed an increasing upward trend and neurological evaluation helped to rule out the possibility of Spinal Muscular Atrophy. Subsequently, whole exome sequencing was done which helped identify one copy (heterozygous) of a likely pathogenic variant in the NEB gene, which is associated with Nemaline Myopathy Type 2 (NEM2), a recessive neuromuscular condition.

In view of poor respiratory effort, we trained the parents for home ventilation and was discharged on noninvasive ventilation at home, along with referral to a multidisciplinary team including neurologist, physiotherapist, nutritionist and Gastroenterologist.

Discussion

Nemaline myopathy (NM) is a clinically and genetically heterogeneous group of congenital myopathies characterized histologically by the presence of nemaline bodies that are rod-shaped, Z-line-derived structures within skeletal muscle fibers, detectable by light and electron microscopy [3,6,7]. The condition presents with a broad spectrum of severity, ranging from severe neonatal forms with respiratory insufficiency and early mortality to milder, slowly progressive forms manifesting in late childhood or adulthood [7,8].

The patient described in this report presented with neonatal hypotonia, consistent with classic features of NM described in the literature. Hypotonia, muscle weakness, and diminished or absent deep tendon reflexes are hallmark findings. Dysmorphic features such as a high-arched palate, facial weakness, and pectus excavatum are common, and musculoskeletal anomalies, including joint contractures, scoliosis, and pes planus, may also be observed [8]. Creatine kinase levels are typically normal, which, although nonspecific, helps distinguish NM from dystrophic myopathies [3].

Respiratory complications are frequently encountered in NM, especially in the more severe phenotypes. While involvement of the cardiac and renal systems is rare, secondary effects due to musculoskeletal abnormalities have been reported. Notably, ophthalmoplegia, while uncommon in most congenital myopathies, may be present in NM and serve as a differentiating clinical clue [12].

Genetically, NM is most commonly caused by mutations in the *NEB* and *ACTA1* genes. *NEB*, which encodes the giant sarcomeric protein nebulin, is typically associated with autosomal recessive inheritance. The majority of pathogenic *NEB* mutations are compound heterozygous frameshifts. This genetic heterogeneity complicates molecular diagnosis, as many mutations are private (unique to a single family) and may be missed by massive parallel sequencing (MPS) due to limitations in coverage or detection sensitivity. In contrast, *ACTA1* mutations, which affect skeletal muscle α-actin, account for a significant proportion of dominant NM cases, including up to 25% of typical forms and nearly 50% of lethal neonatal forms [6,11].

Despite similarities in clinical presentation, NM patients often exhibit distinct patterns of disease progression and histologic features, even within the same family. For example, intrafamilial variability was observed in a family harboring an *ACTA1* missense mutation, where the mother exhibited mild limb-girdle weakness while her child had more classical features such as myopathic facies, high-arched palate, lumbar hyperlordosis, and motor delay [6,10].

In this case, the diagnosis was initially suspected based on clinical presentation and confirmed by whole exome sequencing. This case reinforces the utility of combining histopathological evaluation with next-generation sequencing techniques for accurate diagnosis and subclassification of NM.

Management remains supportive and multidisciplinary, focusing on respiratory care, nutritional support, physiotherapy, and neurological interventions. Early diagnosis not only guides clinical care but also enables appropriate genetic counseling and informs prognosis [12,13].

Conclusion

Nemaline myopathy represents a complex, genetically diverse group of congenital myopathies with variable clinical presentations. This case highlights the importance of recognizing early signs such as neonatal hypotonia, respiratory weakness, feeding difficulties, and delayed motor milestones, which warrant further investigation through muscle biopsy and genetic testing. While there is currently no curative treatment, timely multidisciplinary care can significantly improve quality of life and functional outcomes. Continued reporting of such cases contributes to a deeper understanding of the genotype-phenotype spectrum and the evolving natural history of this rare disorder.

Bibliography

1. Laitila Jenni., *et al*. "Recent advances in nemaline myopathy". *Neuromuscular Disorders* 31.10 (2021): 955-967.

2. Sewry CA., *et al*. "Nemaline myopathies: a current view". *Journal of Muscle Research and Cell Motility* 40.2 (2019): 111-126.

3. Christophers B., *et al*. "Pediatric nemaline myopathy: A systematic review using individual patient data". *Journal of Child Neurology* 37.7 (2022): 652-663.

4. Nance JR., *et al*. "Congenital myopathies: an update". *Current Neurology and Neuroscience Reports* 12.2 (2012): 165-174.

5. Malfatti E and Romero NB. "Nemaline myopathies: state of the art". *Revista Neurologique* 172.10 (2016): 614-619.

6. Wen Q., *et al*. "A childhood-onset nemaline myopathy caused by novel heterozygote variants in the nebulin gene with literature review". *Acta Neurologica Belgica* 120.6 (2020): 1351-1360.

7. Skyllouriotis ML., *et al*. "Nemaline myopathy and cardiomyopathy". *Pediatric Neurology* 20.4 (1999): 319-321.

8. Mubaraki AA. "Nemaline myopathy: A case report". *Case Reports in Neurology* 13.2 (2021): 499-503.

9. Alghanmi BM., *et al*. "A case of a newborn with nemaline myopathy from Al-Qunfudhah city, Saudi Arabia". *Cureus* 16.1 (2024): e52523.

10. Bevilacqua JA., *et al*. "Congenital nemaline myopathy with dense protein masses". *Journal of Neuropathology and Experimental Neurology* 81.4 (2022): 304-307.

11. Shammas I., *et al*. "Filamin C-associated nemaline myopathy". *Neurology* 102.10 (2024): e209477.

12. Romero NB., *et al*. "Recent advances in nemaline myopathy". *Current Opinion in Neurology* 26.5 (2013): 519-526.

13. Moreno CAM., *et al*. "Clinical manifestation of nebulin-associated nemaline myopathy". *Neurology. Genetics* 9.1 (2023): e200056.

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