

## An unusual case of Nemaline Myopathy type 3

### **ABSTRACT**

**Objective:** To report an interesting case of Nemaline Myopathy type 3 with alpha-actin1 (*ACTA1*) mutation.

**Background:** Nemaline myopathy (NM) is a rare congenital neuromuscular disorder that presents with facial weakness, bulbar symptoms, generalized muscle weakness, delayed motor development, hypotonia, and the diagnostic presence of rod-like structures in skeletal muscle biopsy. Currently, eleven different genetic mutations are associated with NM. Dominant and recessive mutations in the  $\alpha$ -actin1 (*ACTA1*) gene are amongst the most frequent genetic cause of nemaline myopathy leading to different clinical phenotypes.

**Case description:** We present a 27-month-old girl with global developmental delay, muscle weakness, and reflux. She was born at 38 weeks. At two months of age, her floppiness and lack of movement were noticed. Since then, she has been started on strict physical, occupational, speech, and behavioral therapy. She began sitting up at age one and started walking at 18 months. Currently, her motor functions are improving. She can say 1-2 words and is interactive with other children. Neurological examination showed a high arched palate with bilateral facial weakness and decreased muscle tone in all the extremities. Muscle strength was 4/5 in bilateral upper and lower extremities. Her gait was narrow-based with bilateral arm swing. She was able to sit and stand without assistance.

**Conclusion:** Symptom management is the basis of patient care in nemaline myopathy. However, as seen in this case, aggressive physical and speech therapy can lead to better motor function and quality of life in congenital myopathies and should be considered.

Keywords: Nemaline Myopathy, Child neurology, Neuromuscular disorder

### **Background**

Nemaline myopathy (NEM) is a collection of congenital myopathies with Nemaline rod or Nemaline body structures that turn red using modified Gömöri trichrome stain or blue with toluidine blue stain (1). The range of clinical manifestations of the disease varies, with males and females being affected equally by nemaline myopathy. *NEM* can be congenital or have an adult-onset. The genetic presentations are due to mutations in *TPM3*, *ACTA1*, *TNNT1*, *KBTBD13*, *KLHK40*, *NEB*, *MYPN*. Mutations in *TPM2*, *CFL1*, *CFL2*, *KLHL40*, *KLHL41*, and *LMOD3* have also been reported to be rarer in occurrence. *NEM* type 3 is discussed in this report and occurs due to mutations in *ACTA1*. The onset of *NEM* type 3 is variable, with mild cases only involving muscular weakness and no other cardiac abnormalities. Severe cases manifest with brain maldevelopment, hepatomegaly, skeletal dysplasia, and urinary tract stenosis.

### **Introduction**

*NEM* is defined by grouping clinical, histological, and genetic features. Muscle magnetic resonance imaging (MRI) is an effective diagnostic tool, revealing muscle involvement connected with mutant genes (3). Histological elements are essential in guiding analysis (1), but the increased use of gene panels and exome sequencing has recognized new genes. It contains

mutations in many genes (at least 12) connected with their existence in muscle biopsies. Additional diagnostic features such as nucleic rods, caps, fiber type imbalance, or disproportion (FTD) have also been described. Intranuclear rods, clumped filaments, cores, or fiber-type disproportion are all available pathologic features essential in the pathogenesis of a specific congenital myopathy.

The occurrence of limited fibers with rods can be misclassified with other congenital myopathy and doubt the current classification of the myopathies. The extensive genomic sequencing leads to increased recognition of clinical phenotypes related to genetic defects such as mutations in the *ACTA1* gene that lead to the formation of rods due to the alpha-actin gene. Nemaline myopathy type 3 (NEM3) is a form of rare myopathy with the normal distribution of muscular weakness with milestones that are delayed but completed eventually also being the second most common cause of Nemaline Myopathy. It is usually a non-progressive to a slowly progressive with a childhood-onset (2). NEM has Nemaline rods that are not unique to nemaline myopathy. The rods occur in muscle-tendon junctions, normal extraocular muscles in the eye, muscles of aging patients, with possible other hereditary or acquired neuromuscular pathologies (2). In vitro, experimental studies demonstrated that rods are present due to metabolic stress due to the exhaustion of adenosine triphosphate (2). Cases in adults have been recorded with sporadic late stages and not inherited. Moreover, a few patients might never arrive at the hospital till adulthood, though physical examination and laboratory tests often identify minor cases in childhood problems (4).

## Patient and Method

The patient was a 27-month-old girl presented at the ocean view clinic. She was clinically assessed, and appropriate lab tests were conducted. She was genetically tested at LA children's hospital. The patient was provided written informed consent. All methods were approved by the National Human Genome Research Institute (NHGRI) central Institutional Review Board. The general assertion criteria for variant classification are publicly available on the GeneDx ClinVar submission page ([HTTP:// www.ncbi.nlm.nih.gov/clinvar/submitters/26957/](http://www.ncbi.nlm.nih.gov/clinvar/submitters/26957/)). She has continued her treatment and therapy at the regional center.

## Case

A two-year three-month-old girl presented to the clinic with a history of global developmental delay, muscle weakness, and reflux came for an initial evaluation after genetically testing positive for an A-G missense mutation in *ACTA1* protein consistent with a diagnosis of nemaline myopathy type 3 (NEM3). She was born prematurely at thirty-eight weeks with meconium aspiration followed by intubation, oxygen chamber treatment, and an initial seven-day NICU stay. The patient was negative for any pathologies at birth. At two months of age, the patient's notable floppiness and lack of movement led to a diagnosis of torticollis and physical therapy. The patient sways when stabilized and has recently increased her core strength. Starting at three months, the patient has undergone continued rehabilitation. She initially was performing at 50% delay for her age but has recently caught up developmentally. In terms of Motor development, she started sitting up at 1yr old, walking at 17-18 months, and currently at 2yrs old, attempts to run with occasional accidents. She sometimes toe-walks with marked improvements in motor capability. Cognitively, she is interactive with other children, and she can say 1-2 words but babbles continuously. She was not making eye contact early on but was diagnosed with strabismus, currently wearing corrective prism lenses as a result. Systemic examination revealed only a cough due to URI. Neurological examination revealed the patient being held with a

bilateral drooping face and slouched posture. When set down, she becomes upright and can walk. She is playful, interactive, babbling, and follows simple commands. A decrease in tone was noted on the patient's face and all appendages. Muscle strength was 4/5 in bilateral upper and lower extremities. A narrow based-gait and bilateral arm swinging were observed. Overall global development delay is noted. Per speech therapy reports, she pools excessive saliva in lateral sulci and is mildly delayed with possible apraxia in expressive and receptive language. The prognosis is favorable due to a diligent regimen of therapy. Lab reports are yet to reveal anything of significance.

The patient presented with Nemaline Myopathy type 3 after testing positive for A-G missense mutation in *ACTA1* protein. The patient's clinical manifestations, including global development and neurological delays, were consistent NM. In this case, it was observed that aggressive physiotherapy and speech therapy can lead to improved motor performance and quality of life for congenital myopathy and should be considered in treatment plans.

## Discussion

NEM3 is due to autosomal dominant, autosomal recessive, or sporadic de novo mutations in alpha-actin. It is mild as it rarely affects cardiac muscles but may affect respiratory muscles in some individuals in the 5th decade of life. Though it could be severe, it does not affect cognitive development. Cardiac involvement is highly uncommon. Even if there are no previous symptoms of cardiomyopathy, the myocardium can be impacted by dilated cardiomyopathy, and the conduction system can be affected by arrhythmias and conduction abnormalities. There was a link between NM and hypertrophic or dilatative cardiomyopathy (20). *ACTA1* is the most frequent gene associated with dominant cases of NEM, which account for 15% to 25% of individuals with typical forms and around 50% with lethal forms. Most cases are dominantly inherited or de novo dominant, while recessive cases are mainly *ACTA1* nulls (5). There is no cure, although an interdisciplinary approach by managing symptoms and rehabilitation leads to maintaining freedom of activities in daily life by exercising and rehabilitation. Supervising vitals to treat orthopedic issues is essential (6, 7).

Inadequate therapeutic effects were recorded with tyrosine (8) even in studies on either the Nemaline myopathy TgACTA1D286G mouse model or the zebrafish model with identical mutations (9,10). Additional amino acid supplements used with zebrafish did not clearly show any net encouraging results (10). The increased upregulation of cardiac actin followed by improvements in skeletal Acta1 knockout mice (11) are expected to have a therapeutic impact on patients but require an early prompt initial diagnosis. Another treatment option was to increase the percentage of ordinary actin in heterozygous cases (12, 13). Genetic compensation noted a milder phenotype in a zebrafish morpholino knock-down model of *ACTA1* nemaline myopathy (14). Acta1 experimental studies of myostatin in two mouse models of nemaline myopathy did not produce more muscular mice, but the TgACTA1D286G mouse model (15) increased body size. In Acta1H40Y mice, a similar study was conducted on the model, leading to an increase in size and longer lifespan (16). The utilization of myosin transgene leads to better muscle utility in the Acta1 mouse model (17). The utilization of calcium sensitizers leads to better diaphragmatic functioning (18, 19).

Mild forms of NM can be successfully treated, and the patient's muscle function can be restored. In more severe cases, however, the consequence may be unfavorable. Reduced muscle function can lead to significant physical limitations, and the patient may use a wheelchair for the rest of their life. Because of the difficulties that can arise from the illness, it could be fatal. NEM has a

short life expectancy, with most patients living only 2 to 3 years. Individuals with less severe types, on the other hand, can live an everyday life provided they receive regular rehabilitative treatment. Genetic counseling and gene reviews can help couples in family planning. Several organizations and support groups can help patients cope while spreading awareness of the disease (5).

## Conclusion

With this case, we can understand effective and diligent rehabilitative therapy with follow-ups would help alleviate the symptoms of myopathy. Communication skills can be enhanced through speech therapy, oral prostheses, surgery, and assistive devices. People with NM are usually very sociable, intelligent, and need to communicate. Hypoventilation is subtle and can induce issues in health. Hence it is corrected with non-invasive mechanical devices to provide support at night. Patients can develop scoliosis, which progresses in childhood and deteriorates in puberty. Many people with NM undergo spinal fusion to straighten out and steady their back (20). As we appreciate and recognize the pathogenic mechanisms and treatment options studied so far, Future studies of nemaline myopathy are required with international patient enrollment. Thus, international cooperation would lead to treatment trials for harmless and therapeutically efficient treatments that become accessible over time.

### **Conference disclaimer:**

“Some part of this manuscript was previously presented and published in the following conference.

Conference name: 143rd Annual Meeting American Neurological Association

Dates and location : Atlanta, GA Oct 21-23, 2018 at Hyatt Regency Atlanta

Web Link of the proceeding: <https://onlinelibrary.wiley.com/doi/full/10.1002/ana.25331>

### **Ethical Approval:**

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

### **Consent**

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## References

- 1.) Dubowitz V, Sewry CA, Oldfors A. Muscle biopsy: a practical approach. 4. Oxford: Elsevier; 2013.
- 2.) Vandebrouck A, Domazetovska A, Mokbel N, Cooper ST, Ilkovski B, North KN. In vitro analysis of rod composition and actin dynamics in inherited myopathies. *J Neuropathol Exp Neurol*.
- 3.) Jungbluth H. Myopathology in times of modern imaging. *Neuropathol Appl Neurobiol*. 2017; 43:24–43
- 4.) Schnitzler LJ, et al. Sporadic late-onset nemaline myopathy: clinico-pathological characteristics and review of 76 cases. *Orphanet J Rare Dis*. 2017; 12:86
- 5.) Matthew Harmelink, M. D. (2019, November 10). Congenital myopathies clinical presentation: History, Nemaline Rod Myopathy, core myopathy. *Congenital Myopathies Clinical Presentation: History, Nemaline Rod Myopathy, Core Myopathy*. Retrieved November 22, 2021, from <https://emedicine.medscape.com/article/1175852-clinical>.
- 6.) 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders -- congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II) 4-6 April 2003, Naarden, The Netherlands. Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A, ENMC. *Neuromuscul Disord*. 2004 Jan; 14(1):56-69.
- 7.) Consensus statement on standard of care for congenital myopathies. Wang CH, Dowling JJ, North K, Schroth MK, Sejersen T, Shapiro F, Bellini J, Weiss H, Guillet M, Amburgey K, Apkon S, Bertini E, Bonnemann C, Clarke N, Connolly AM, Estournet-Mathiaud B, Fitzgerald D, Florence JM, Gee R, Gurgel-Giannetti J, Glanzman AM, Hofmeister B, Jungbluth H, Koumbourlis AC, Laing NG, Main M, Morrison LA, Munns C, Rose K, Schuler PM, Sewry C, Storhaug K, Vainzof M, Yuan N *J Child Neurol*. 2012 Mar; 27(3):363-82
- 8.) Dietary L-tyrosine supplementation in nemaline myopathy. Ryan MM, Sy C, Rudge S, Ellaway C, Ketteridge D, Roddick LG, Iannaccone ST, Kornberg AJ, North KN *J Child Neurol*. 2008 Jun; 23(6):609-13.
- 9.) L-tyrosine supplementation does not ameliorate skeletal muscle dysfunction in zebrafish and mouse models of dominant skeletal muscle  $\alpha$ -actin nemaline myopathy. Messineo AM, Gineste C, Sztal TE, McNamara EL, Vilmen C, Ogier AC, Hahne D, Bendahan D, Laing NG, Bryson-Richardson RJ, Gondin J, Nowak KJ *Sci Rep*. 2018 Jul 31; 8(1):11490
- 10.) Testing of therapies in a novel nebulin nemaline myopathy model demonstrate a lack of efficacy. Sztal TE, McKaige EA, Williams C, Oorschot V, Ramm G, Bryson-Richardson RJ *Acta Neuropathol Commun*. 2018 May 30; 6(1):40.
- 11.) Rescue of skeletal muscle alpha-actin-null mice by cardiac (fetal) alpha-actin. Nowak KJ, Ravenscroft G, Jackaman C, Filipovska A, Davies SM, Lim EM, Squire SE, Potter AC, Baker E, Clément S, Sewry CA, Fabian V, Crawford K, Lessard JL, Griffiths LM, Papadimitriou JM, Shen Y, Morahan G, Bakker AJ, Davies KE, Laing NGJ *Cell Biol*. 2009 Jun 1; 185(5):903-15.
- 12.) Ravenscroft G, et al. Mouse models of dominant ACTA1 disease recapitulate human disease and provide insight into therapies. *Brain*. 2011; 134:1101–1115.

- 13.) Ravenscroft G, Jackaman C, Sewry CA, et al. Actin nemaline myopathy mouse reproduces disease, suggests other actin Disease phenotypes and provides cautionary note on muscle transgene expression. *PLoS ONE*. 2011;6(12): e28699
- 14.) Genetic compensation triggered by actin mutation prevents the muscle damage caused by loss of actin protein. Sztal TE, McKaige EA, Williams C, Ruparella AA, Bryson-Richardson RJ *PLoS Genet*. 2018 Feb; 14(2): e1007212.
- 15.) Myostatin inhibition using mRK35 produces skeletal muscle growth and tubular aggregate formation in wild type and TgACTA1D286G nemaline myopathy mice. Tinklenberg JA, Siebers EM, Beatka MJ, Meng H, Yang L, Zhang Z, Ross JA, Ochala J, Morris C, Owens JM, Laing NG, Nowak KJ, Lawlor MW *Hum Mol Genet*. 2018 Feb 15; 27(4):638-648.
- 16.) Treatment with ActRIIB-mFc Produces Myofiber Growth and Improves Lifespan in the Acta1 H40Y Murine Model of Nemaline Myopathy. Tinklenberg J, Meng H, Yang L, Liu F, Hoffmann RG, Dasgupta M, Allen KP, Beggs AH, Hardeman EC, Pearsall RS, Fitts RH, Lawlor MW *Am J Pathol*. 2016 Jun; 186(6):1568-81.
- 17.) Lindqvist J, Levy Y, Pati-Alam A, Hardeman EC, Gregorevic P, Ochala J. Modulating myosin restores muscle function in a mouse model of nemaline myopathy. *Ann Neurol*. 2016; 79:717–725.
- 18.) Ca<sup>2+</sup> sensitizers: An emerging class of agents for counterbalancing weakness in skeletal muscle diseases? Ochala J *Neuromuscul Disord*. 2010 Feb; 20(2):98-101.
- 19.) Doorduyn J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, Heunks LM. The calcium sensitizer levosimendan improves human diaphragm function. *Am J Respir Crit Care Med*. 2012; 185:90–95.
- 20.) Bionity.com. 2021. Nemaline\_myopathy. [online] Available at: <[https://www.bionity.com/en/encyclopedia/Nemaline\\_myopathy.html](https://www.bionity.com/en/encyclopedia/Nemaline_myopathy.html)> [Accessed 23 November 2021].