



ACTA1 Mutation Related Nemaline Myopathy in a Newborn - A Report on a Child with a Novel Mutation

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Abstract

A diagnosis of congenital myopathy, including nemaline myopathy, is an important consideration in babies born with hypotonia. We report a novel mutation in the ACTA1 gene in a child diagnosed with nemaline myopathy.

Keywords: Nemaline; Myopathy; ACTA1

Introduction

ACTA1 mutations can cause severe congenital myopathy presenting with early onset hypotonia and weakness. Although ACTA1 related myopathies present clinically with some features of nemaline myopathies and some of core and fiber-type disproportion myopathies, they are generally thought of as part of the nemaline myopathy group. ACTA1 mutations are associated with up to 25% of cases with nemaline myopathy and in up to 50% of patients with severe or fatal cases [1-3]. Here, we report a case of a very severely affected newborn with a novel ACTA1 mutation.

Case Presentation

To collate this report we reviewed the patient's electronic medical record and performed a relevant literature search.

This male baby was born at 36 weeks gestation by cesarean section for polyhydramnios and a non-reassuring fetal heart rate. The birth weight was 2194 grams. The child did not have any respiratory effort at birth. He was intubated and mechanical ventilation was started. On examination, the child was severely hypotonic and showed very little active movement other than slight finger flexion. Deep tendon reflexes were barely elicited, with just a flicker of muscle contraction. He had no upper motor neuron signs. He had micrognathia, retrognathia, low set ears, a small mouth and an upturned nose. He also had a sacral tuft of hair, wide-spaced nipples, thin ribs (Figure 1), rocker bottom foot on the left as well as a club foot and hyper extended knee on the right. Both hands showed ulnar clinodactyly of the index finger and radial clinodactyly of the second through fifth digits. The distal phalanges appeared narrow proximally and were spade shaped distally. His right testis was high and the left could not be palpated in the scrotum. Emergency karyotype and the SNP microarray were normal. Head ultrasound did not show any abnormalities but on sacral ultrasound, the conus was found to be low lying at the level of L4-L5, which along with the sacral tuft of hair suggested the presence of a tethered cord. Inguinal ultrasound showed the child's left testis to be present but lying in middle of the left inguinal canal. A magnetic resonance imaging of the brain showed a thin subdural hematoma along the right occipital lobe and along the tentorium. There was no mass effect or midline shift and the brain was found to be normal in morphology without signal abnormality. The subdural hematoma was thought to not be significant and was not surgically evacuated. Echocardiogram showed a large and patent ductus arteriosus and a small but patent foramen ovale. Ventricles were slightly dilated bilaterally. CPK levels were high at 377 on day 6 of life but were relatively normal at 98 when retested at 24 days of life. A skeletal survey at day 6 of life showed an acute fracture of the left mid femur with lateral apex angulation (Figure 2). The skeletal survey also showed areas of increased bone mineral density (osteosclerosis) though all the long tubular bones were very thin and gracile in appearance and these may have represented response to previous fracture. The child's course was complicated because of the persistent respiratory failure. An initial chest X-ray showed an elevated right hemi diaphragm (Figure 1). A chest ultrasound at day 7 of life, confirmed right hemi diaphragm paralysis. The course was further complicated by right lung atelectasis and accidental extubation with subsequent aspiration pneumonia. The child was re-intubated but then developed bilateral pleural effusion. The right sided pleural effusion

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Figure 1: An initial chest X-ray showed an elevated right hemi diaphragm.



Figure 2: An acute fracture of the left mid femur with lateral apex angulation.

persisted for several days and when it subsequently increased, it required evacuation via chest tube. Worsening respiratory status necessitated high frequency jet ventilation. Worsening pulmonary hypertension was treated with sildenafil and inhaled nitric oxide. Nitric oxide was eventually successfully weaned off. However, the child failed all attempts at extubation over his approximately 5 month neonatal ICU course. Given that a unifying diagnosis was not readily available; whole exome sequencing was ordered [4]. This revealed an ACTA1 gene mutation with p. Gly148Arg (GGC>CGC):c. 442G>C in exon 3. Mom, who was unaffected, was found to be a mosaic for the same mutation. A muscle biopsy from the quadriceps was also abnormal on cytopathology with prominent atrophic myofiber population in small groups. Nemaline rods were inconspicuous on light-microscopic examination so it was not considered diagnostic of nemaline myopathy (Figure 3), however, upon electron microscopic examination (Figure 4) they were more readily apparent but in a much disorganized formation. Due to somewhat increased mitochondrial content, mitochondrial sequencing was also performed and was unremarkable; this was thought to be compensatory in nature. Sadly, the child passed away at around 5 months of life subsequent to the family and staff reaching a decision to withdraw ventilator support due to the severe and chronic nature of the disease with significant as well as ongoing functional limitation in several organ systems, lack of any observable improvement in muscle strength, and inability to wean from ventilation. Attempting right diaphragmatic plication was not thought to be prudent or feasible.

Discussion

Nemaline myopathy is a congenital myopathy with the presence of rod-shaped aggregates as a distinct histological hallmark, with genetically heterogeneous etiology. Mutations that disrupt the structure or function of several myofibrillar and myofibrillar-associated proteins have been associated with this condition [1-3,5]. Most of the clinical and histologic features seen with our patient have been reported in other children affected by ACTA1 mutation nemaline myopathy. As mentioned earlier, ACTA1 mutations are a

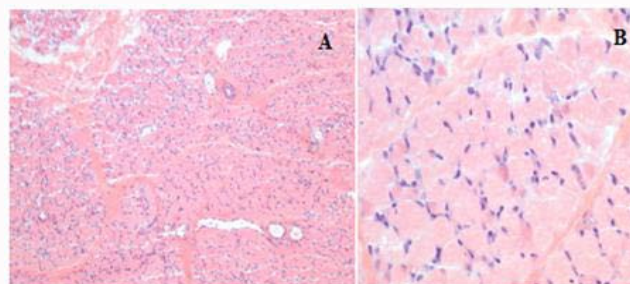


Figure 3: Nemaline rods were inconspicuous on light-microscopic examination.

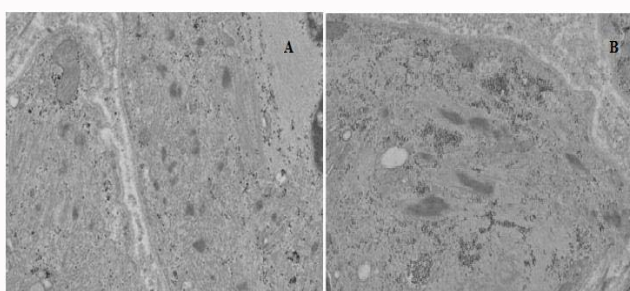


Figure 4: After microscopic examination increased mitochondrial content.

leading cause of the more severe presentations of nemaline myopathy [1-3,5]. Severe nemaline myopathy can be associated with respiratory muscle weakness and as in this case, demonstrate intrauterine effects on growth and development due to immobility, which was reported in retrospect by this child's mother [6]. Besides nemaline myopathy, ACTA1 mutations with milder effects can also cause myopathy with Congenital Fiber-Type Disproportion (CFTDM) and can cause either dominant or recessive disease [7,8]. This case is significant as the child had a novel, previously unreported mutation in the ACTA1 gene, which is almost certainly pathogenic. Mutation Taster indicates that amino acid is strongly conserved, is not a known variant, has effects on splice site and gives a significant disease causing rating of 0.99999960919345. PROVEAN score was significant at -6.321, and Polyphen score significant at 0.728. Other alterations to different amino acids at that locus have been reported in associated with severe disease. Usually AD cases of this severity are de novo, but as in this case, a seemingly unaffected parent with a low level mosaicism for the mutation may have a severely affected child with a 50% dose [9-16].

Conclusion

We would urge practitioners to strongly consider congenital myopathy for weak floppy babies, especially those with non-neurogenic features, multiple dimorphisms including congenital contractures and fragility fractures, and mild CPK elevation. Next-generation panels and exome sequencing should be used for specific genetic diagnosis. Electron microscopy should be obtained on muscle biopsy if the light microscopy is normal. ACTA1 cases tend to be more severe than other causes of nemaline myopathy but both presentation as well as inheritance can vary.

References

1. Moreno CDAM, Neto OA, Donkervoort S, Hu Y, Reed UC, Oliveira ASB, et al. Clinical and Histologic Findings in ACTA1-Related Nemaline Myopathy: Case Series and Review of the Literature. *Pediatr Neurol*. 2017;75:11-6.

2. North KN, Ryan MM. Nemaline myopathies. *Gene Reviews*. 2015.
3. Donkervoort S, Chanb SHS, Hayes LH, Bradley N, Nguyen D, Leach ME, et al. Cytoplasmic body pathology in severe ACTA1-related myopathy in the absence of typical nemaline rods. *Neuromuscul Disord*. 2017;27(6):531-6.
4. Borghesi A, Mencarelli MA, Memo L, Ferrero GB, Bartuli A, Genuardi M, et al. Intersociety policy statement on the use of whole-exome sequencing in the critically ill newborn infant. *Ital J Pediatr*. 2017;43(1):100.
5. Wallgren-Pettersson C, Sewry CA, Nowak KJ, Laing NG. Nemaline myopathies. *Semin Pediatr Neurol*. 2011;18(4):230-8.
6. Danhaive O, Lozzi S, D'amico A, Devito R, Boldrini R, Corchia C, et al. Neonatal-onset nemaline myopathy mimicking congenital diaphragmatic hernia. *J Pediatr Surg*. 2007;42(7):19-22.
7. Sparrow JC, Nowak KJ, Durling HJ, Beggs AH, Wallgren-Pettersson C, Romero N, et al. Muscle disease caused by mutations in the skeletal muscle alpha-actin gene (ACTA1). *Neuromusc Disor*. 2003;13(7-8):519-31.
8. Online Mendelian Inheritance in Man[®]. An Online Catalog of Human Genes and Genetic Disorders. 2019.
9. Laing N, Nowak K. Global Variome shared LOVD ACTA1. 2019.
10. Schwarz JM, Cooper DN, Schuelke M, Seelow D. Mutation Taster2: mutation prediction for the deep-sequencing age. *Nat Methods*. 2014;11(4):361-2.
11. Choi Y, Sims GE, Murphy S, Miller JR, Chan AP. Predicting the Functional Effect of Amino Acid Substitutions and Indels. *PLoS One*. 2012;7(10):46688.
12. Choi Y, Chan AP. PROVEAN web server: a tool to predict the functional effect of amino acid substitutions and indels. *Bioinformatics*. 2015;31(16):2745-7.
13. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;7(4):248-9.
14. Elizabeth Taylor DeChene, Peter B Kang, Alan H Beggs. Congenital Fiber-Type Disproportion. *Gene Review*. 2013.
15. Kathryn N North, Monique M Ryan. Nemaline Myopathy. *Gene Reviews*. 2015.
16. Laing NG, Dye DE, Wallgren-Pettersson C, Richard G, Monnier N, Lillis S, et al. Mutations and polymorphisms of the skeletal muscle alpha-actin gene (ACTA1). *Hum Mutat*. 2009;30(9):1267-77.