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Neonatal Fractures as a Presenting Feature of *LMOD3*-Associated Congenital Myopathy

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Abstract

Nemaline myopathy is a rare inherited disorder characterized by weakness, hypotonia and depressed deep tendon reflexes. It is clinically and genetically heterogeneous, with the most severe phenotype presenting as perinatal akinesia, severe muscle weakness, feeding difficulties and respiratory failure, leading to early mortality. Pathogenic variants in twelve genes, encoding components of the sarcomere or factors related to myogenesis, have been reported in patients affected with the disorder. Here, we describe an early, lethal presentation of decreased fetal movements, hypotonia, muscle weakness, and neonatal respiratory failure requiring ventilator support in three siblings from a consanguineous family. All exhibited perinatal fractures, and thus, a skeletal dysplasia was considered as possibly contributing to the phenotype. However, whole exome sequencing revealed a homozygous, loss-of-function pathogenic variant in *LMOD3*, which has recently been associated with nemaline myopathy and, in a subset of patients, perinatal fractures. This case demonstrates the importance of considering congenital neuromuscular disorders in the differential diagnosis of perinatal fractures.

Keywords

LMOD3; congenital fractures; nemaline myopathy; congenital myopathy; perinatal fractures

INTRODUCTION

Nemaline myopathy (NM) is a rare genetic disorder that primarily affects skeletal muscle resulting in generalized weakness, which is typically proximal in location, hypotonia and depressed deep tendon reflexes. This congenital myopathy is characterized by an accumulation of nemaline bodies, which are rod-like inclusions located inside the myofibers

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that can be detected by Gomori trichome staining [Wallgren-Pettersson et al 2011]. The phenotypic spectrum ranges from mild, adult-onset to severe congenital forms [Wallgren-Pettersson et al 2011]. The congenital type comprises approximately 16% of all NM cases [Ryan et al 2001] and classically presents with decreased fetal movements, severe hypotonia, muscle weakness, feeding difficulties and respiratory insufficiency in the neonatal period [Ryan et al 2001]. In contrast to earlier-onset forms, adult-onset forms typically occur sporadically and may be associated with monoclonal gammopathy of unknown significance [Schnitzler et al 2017].

NM is genetically heterogeneous, and pathogenic variants in twelve genes have been associated with this disorder [Gurung et al 2017; Malfatti et al 2015; Massalska et al 2016; Miyatake et al 2017; Seferian et al 2016]. Pathogenic variants in six of these genes (*NEB, ACTA1*, *TPM3*, *KLHL40*, *KLHL41*, and *LMOD3*) have been associated with the severe congenital phenotype [Gupta et al 2013; Nowak et al 1999; Pelin et al 1999; Ravenscroft et al 2013; Tan et al 1999; Yuen et al 2014]. The inheritance pattern for severe congenital NM is typically autosomal recessive (*NEB, TPM3, KLHL40, KLHL41*, and *LMOD3*) with occasional autosomal dominant inheritance (*ACTA1).* Pathogenic variants in *LMOD3* were recently identified as a genetic cause of NM. In the only published report of NM caused by pathogenic variants in *LMOD3*, 90% of the patients were identified as having severe congenital NM [Yuen et al 2014]. *LMOD3* encodes for a protein known as leiomodin-3, which is located in the actin thin filaments of skeletal and cardiac muscle. Deficiency of leimodin-3 results in disorganization of thin filaments, decreased muscle function, and nemaline bodies with unique morphology [Yuen et al 2014].

Here, we describe a consanguineous family whose three daughters presented with decreased fetal movements, hypotonia, muscle weakness, respiratory distress, and long bone fractures noted at birth. The three siblings died within days after birth due to respiratory insufficiency. Given the finding of fractures at birth, osteogenesis imperfecta was considered in the differential diagnosis. However, using whole exome sequencing (WES), the subjects were later confirmed to have a homozygous pathogenic variant in *LMOD3* and were diagnosed postmortem with severe congenital myopathy, which is presumed to be NM, although tissue was not available to confirm the presence of nemaline bodies. There is only one previous report describing a cohort of 21 individuals from 14 families with a pathogenic variant in *LMOD3* causing congenital myopathy or confirmed NM but only two of the subjects in this report had fractures [Yuen et al 2014]. The cases described in our report demonstrate that fractures can be a prominent finding in *LMOD3*-associated congenital myopathy and demonstrates the importance of considering NM when evaluating neonates with congenital fractures.

CLINICAL REPORT

The probands are of Turkish descent and were the offsprings of consanguineous parents (first cousins) (Figure 1). Neither parent had a history of fractures. In addition to the three probands, the couple had one spontaneous pregnancy loss.

Proband II.1 was a female born at 36 weeks gestation via cesarean section. Birth weight was 1900 g (4th centile), and length was 42.5 cm (6th centile). During pregnancy the mother noted decreased fetal movements. Apgar scores were 3 at 1 minute and 6 at 5 minutes of life. She was not breathing spontaneously and was taken to the intensive care unit. On exam, depressed nasal bridge and sparse eyebrows (interior portion) were noted. She also had absent suck, absent Moro reflex, muscle weakness, severe hypotonia and diffuse edema. Bilateral fractures of her humeri and a fracture of the right femoral diaphysis were noted. She required ventilator support from birth until she died 3 days later due to respiratory compromise.

Proband II.2 was a female born at 33 weeks gestation. Birth weight was 2050 g (65th centile), and length was 43 cm (55th centile). Mother reported decreased fetal movements during the pregnancy. On exam, she had a wide forehead, sparse interior portion of the eyebrows, anteverted nares, long philtrum, retrognathia, short neck, pectus excavatum, minimal spontaneous movement, absent suck, absent Moro reflex, muscle weakness, and severe hypotonia. She had fractures of the right humerus and left femur (Figure 2). She was not breathing spontaneously and was taken to the intensive care unit, where she was diagnosed with respiratory distress syndrome. She required ventilator support from birth until she died at 43 days of age due to respiratory compromise.

Proband II.3 was a female born at 34 weeks and 6 days. The pregnancy was complicated by polyhydramnios and diffuse fetal edema noted at 31–32 weeks gestation. Birth weight was 1890 g (14^{th} centile), and length was 42 cm (12^{th} centile). On exam, she had diffuse edema, down slanting palpebral fissures, anteverted nares, depressed nasal bridge, thin and smooth philtrum, narrow/high palate, absent suck, absent Moro reflex, muscle weakness, and severe hypotonia. In addition, a fracture of the left humerus and pes equinovarus were noted. She required ventilatory support from birth until death at 9 days of age due to respiratory compromise.

MATERIALS AND METHODS

Clinical Studies

Because of the finding of perinatal fractures, the probands' parents were enrolled in a research protocol for skeletal dysplasias that was approved by the Baylor College of Medicine Institutional Review Board (IRB). Informed consent was obtained from both parents prior to participation, including permission for whole exome sequencing and the publication of medical information from their deceased children.

Whole Exome Sequencing

Whole blood samples were obtained from the probands and parents, and DNA was extracted from peripheral blood monocytes for WES. WES was performed on DNA obtained from proband II.2. Briefly, the exome was captured using the HGSC CORE design [Bainbridge et al 2011](52Mb, NimbleGen) according to the manufacturer's protocol *NimbleGen SeqCap EZ Exome Library SR User's Guide* with minor revisions, and sequencing was performed on the Illumina HiSeq 2000 platform (Illumina) [Yang et al 2013]. Sequence reads were

aligned (hg19), processing, variant calling and annotation were completed using the MERCURY pipeline [Reid et al 2014]. Variants were filtered for allele frequency of less than 1% in the ExAC database v0.3 [Lek et al 2016] and 1000 genomes project phase 3 [Genomes Project et al 2015]

Sanger Sequencing

To confirm the variant detected by WES, primers were designed to amplify exon 1 of *LMOD3* (F: GTTAACTGGGGGACCTTCTTG, R: CCAAACCCTGGAGTCTTGAG) in samples from the probands and parents. Polymerase chain reaction was performed using 2 ng/uL of DNA and GoTaq polymerase (Promega, Madison, WI, USA) as per manufacturer's instructions to amplify exon 1 with the primers listed above. PCR products were confirmed using agarose gel electrophoresis. The samples were submitted for Sanger Sequencing (Beckman Coulter Genomics, Danvers, MA, USA) using the same primers.

RESULTS

WES was performed using DNA from proband II.2 and revealed an apparently homozygous, previously reported, pathogenic variant in *LMOD3* (NM_001304418: c.138dupC, p.Ser47GlnfsTer13) [Yuen et al 2014]. This variant was confirmed by Sanger sequencing, and Sanger sequencing confirmed that the proband's affected sibling (II.3) was also apparently homozygous for this same variant. No DNA was available from the other affected sibling (II.1). Sanger sequencing of DNA samples from the parents revealed that both parents are heterozygous for this variant (Fig. 1). No pathogenic variants in known genes associated with low bone mass or osteogenesis imperfecta were identified, and no other pathogenic variants in known myopathy genes were identified.

DISCUSSION

The probands, who presented with decreased fetal movements, muscle weakness, perinatal fractures and respiratory compromise leading to death in early infancy, were found to have a homozygous frameshift pathogenic variant in *LMOD3* that was previously reported in three other subjects with severe congenital NM and that has been previously associated with no protein expression [Yuen et al 2014]. All three probands were critically ill after delivery with diffuse edema, respiratory insufficiency, and abnormal neurologic examination including hypotonia and muscle weakness which is consistent with the phenotype of severe congenital myopathy. None of the three subjects had arthrogryposis which was observed in a subset of subjects in the previously published cohort of individuals with *LMOD3* variants [Yuen et al 2014]. Tissue was not available for histopathologic analysis or electron microscopy to determine if nemaline rods were present. Interestingly, the nemaline rods in *LMOD3*-associated congenital myopathy are unique as compared to those identified in other forms of NM as they appear similar to remnants of the thickened Z-disc with surrounding thin filaments that are shortened [Yuen et al 2014]. In the absence of tissue histology, as in these cases, molecular testing may facilitate a diagnosis.

LMOD3 encodes for a protein known as leiomodin-3 which is expressed in both cardiac and skeletal muscle with highest expression levels in skeletal muscle [Yuen et al 2014]. It is

expressed at early stages of skeletal muscle differentiation, which may be why loss of function typically results in a severe congenital phenotype [Yuen et al 2014].

Loss of this protein results in short and non-functional sarcomeres [Yuen et al 2014]. In a mouse model, loss of leiomodin-3 caused replacement of the sarcomeres by nemaline bodies and glycogen granules, which create an irregular and disorganized myofiber structure [Cenik et al 2015]. Others have shown atrophy of fast twitch muscle fibers in *LMOD3* deficient mice [Tian et al 2015].

Congenital fractures are classically linked to either trauma or osteogenesis imperfecta [Morgan and Marcus 2010]. However, other rare disorders, such as Ehlers-Danlos type VIIC (caused by a pathogenic variant in *ADAMTS2*) can be associated with perinatal fractures [Solomons et al 2013] (Table 1). Particularly, congenital fractures may be observed in disorders associated with decreased fetal movement, such as spinal muscular atrophy (SMA) [Van Toorn et al 2002], or in the fetal akinesia deformation sequence (Pena-Shokeir syndrome)[Chen et al 1995]. Reduced fetal movements have been shown to result in thin, hypomineralized bones that are easily fractured [Lacson et al 2002]. Fetal akinesia decreases the mechanical loading on the developing bone, causing osteopenia [Rodriguez et al 1988a; Rodriguez et al 1988b] and may also be associated with arthrogryposis [Ravenscroft et al 2011]. Together, bone fragility and joint deformities put the newborn at increased risk for *in utero* and neonatal fractures.

Congenital fractures are not uncommon in severe, congenital myopathies. In one study 7/23 cases of severe congenital NM surveyed had congenital fractures [Ryan et al 2001]. Another study demonstrated that 10/19 individuals with severe congenital NM caused by pathogenic variants in *KLHL40* had pathologic fractures [Ravenscroft et al 2013]. The fractures reported in severe congenital NM and neuromuscular diseases predominantly involve long bones (femur/humerus), and in such cases, the bones have been reported to be hypomineralized and thin [Ryan et al 2001], with callus and/or remodeling present, suggesting intrauterine origin [Buonocore et al 1993; Rodriguez et al 1988b]. The predominant explanation for fractures in severe congenital NM is limited fetal movement [Rodriguez et al 1988a], and all three of our probands likely suffered from fetal akinesia secondary to their myopathy. Another theory is that the fractures are sustained on delivery [Hall 2014]. It has historically been recommended that all infants with known arthrogryposis be delivered by cesarean section to reduce the risk of fractures associated with delivery [Hall 2014]. However, a recent study evaluated antenatal outcome in patients with osteogenesis imperfecta who were delivered via cesarean section vs. vaginal delivery and found no difference in fracture rate [Bellur et al 2016]. This study suggested that fracture prevention should not be the sole motivation in choosing cesarean section [Bellur et al 2016]. No conclusive evidence exists as to whether cesarean section results in decreased fracture prevalence in NM when compared to vaginal delivery.

In conclusion, congenital myopathy can present in the neonatal period with congenital fractures. Specifically, this is the second report describing pathogenic variants in *LMOD3* causing a severe congenital myopathy phenotype associated with perinatal fractures [Yuen et al 2014]. It is unclear if some fractures occur or are worsened by delivery, necessitating the

need to handle any infant with a known diagnosis of congenital myopathy, such as NM, with care during delivery and the perinatal period. *LMOD3*-associated congenital myopathy or NM, should be considered in the differential diagnosis for neonatal (or prenatal) fractures especially in the setting of severe hypotonia, to facilitate early diagnosis and the provision of appropriate genetic counseling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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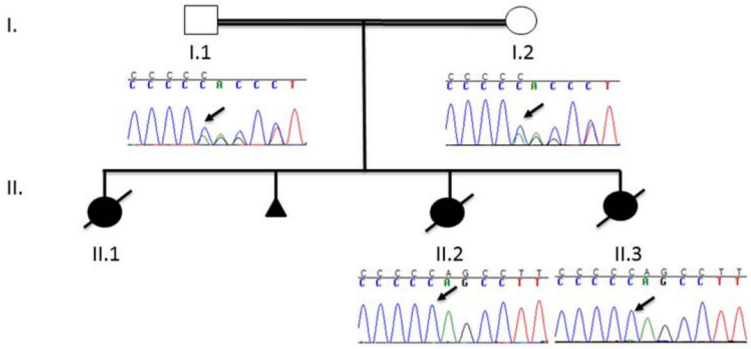

Figure 1.

Pedigree and Sanger sequencing. Sanger sequencing in both parents (first cousins) demonstrated that they are heterozygous for the pathogenic variant in *LMOD3*. Probands II. 2 and II.3 were homozygous for the pathogenic variant in *LMOD3*. Proband II.1 had a similar presentation as probands II.2 and II.3, but DNA was not available for testing.

Table 1

Genetic Differential Diagnosis of Congenital Fractures

Disorder	Inheritance	Typical Location of Fracture	References
Skeletal Dysplasia			
Osteogenesis Imperfecta	AD, AR	Long bones, ribs	[Krakow 2015]; [Morgan and Marcus 2010]
Hypophosphatasia	AD, AR	Ribs	[Kozlowski et al. 1976]; [Bianchi 2015]
Campomelic Dysplasia	AD	Long bones	[Gimovsky et al. 2008]
Osteopetrosis, Malignant Infantile Type	AR	Long bones	[el Khazen et al. 1986]; [Stark and Savarirayan 2009]
Neuromuscular Disorders			
Nemaline Myopathy, Severe Congenital Type	AR	Long bones	[Ryan et al. 2001], [Ravenscroft et al. 2013], [Buonocore et al. 1993], [Lacson et al. 2002]
Prenatal Onset Spinal Muscular Atrophy	AR	Long bones	[Knierim et al. 2016]
Spinal Muscular Atrophy	AR	Long bones	[Van Toorn et al. 2002], [Rodriguez et al. 1988a], [Knierim et al. 2016]
Central Core Disease	AD, AR	Long bones	[Bharucha-Goebel et al. 2013]
X linked Myotubular Myopathy	X linked	Long bones	[Han et al. 2013]
Others			
Ehlers Danlos Syndrome, type VIIC	AR	Skull	[Bar-Yosef et al. 2008], [Solomons et al. 2013]
Antley Bixler Syndrome	AR	Long bones	[DeLozier et al. 1980]; [Robinson et al. 1982]
Amyoplasia	Variable	Long bones	[Hall et al. 2014]
Infantile Myofibromatosis	AD, AR	Femur	[Buonuomo et al. 2006]

Table consists of *representative references* that report congenital fractures in the above conditions. Abbreviations: AD: autosomal dominant; AR: autosomal recessive.