X-Linked Myotubular Myopathy and Duchenne Muscular Dystrophy in a Preterm Infant: A Rare Combination

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abstract

Disorders of central and peripheral nervous system should be considered in floppy infants with ventilator dependence. Workup for neuromuscular disorders should be undertaken in infants with hypotonia, weakness, contractures, feeding difficulties, or failed attempts at extubation. We present the case of a preterm infant with hypotonia and ventilator dependence where despite a positive result, further investigations were undertaken because of lack of clinical correlation. The infant had a rare combination of 2 neuromuscular conditions: X-linked myotubular myopathy and Duchenne muscular dystrophy. One was the reason for immediate clinical manifestation and the other influenced the prognosis and decision-making in determining reorientation of care. This case demonstrates the value of interpretation of a positive result that did not explain the clinical picture and warranted consideration of further diagnosis. This case also emphasizes the importance of discussions with family about the prognosis of 2 conditions that influenced decision making.

Congenital myopathies are a group of heterogeneous rare neuromuscular disorders with distinct histopathological features of rods, cores, central nuclei, and fiber-type disproportion.[1] X-linked myotubular myopathy (XLMTM) is a type of congenital myopathy with incidence of 1:50 000 live male births caused by mutation in the *MTM1* gene.[2] The presentations vary in severity, ranging from fatal forms in infancy to milder phenotypes surviving until adulthood.[3] Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that affects 1 in 3600 to 6000 live male births.[4] Most patients present with delayed motor milestones and progressive motor difficulties with additional respiratory, cardiac complications, and death in the second or third decade. We present the case of a male infant diagnosed with XLMTM and DMD, which constitute a combination of a rare and a more common muscle disorder.

CASE REPORT

This male infant was born prematurely to a primigravida mother at 31 weeks' gestation by cesarean delivery under general anesthesia because of placental abruption and antepartum hemorrhage. The pregnancy was uneventful and there was no history of polyhydramnios. The infant was floppy at birth and showed no respiratory effort but had a good heart rate. He was intubated and given surfactant with a provisional diagnosis of respiratory distress syndrome.

Despite minimal ventilation requirements, the infant continued to

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Drs Varma and Mukherjee collected the information and drafted the initial manuscript; Drs Hughes and Kamupira identified the case; Dr Sethuraman contributed to the valuable histopathology information and provided the images; and all authors reviewed and revised the document and approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2018-2879

Accepted for publication Feb 13, 2020

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Varma U, Mukherjee D, Hughes I, et al. X-Linked Myotubular Myopathy and Duchenne Muscular Dystrophy in a Preterm Infant: A Rare Combination. *Pediatrics.* 2020;146(3):e20182879

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have poor respiratory effort and failed several attempts at extubation and trials of noninvasive ventilation. Direct laryngotracheal bronchoscopy did not reveal any airway abnormalities. The infant remained hypotonic with a paucity of limb movements. He had facial weakness and poor gag and suck reflexes. His deep tendon reflexes were difficult to elicit. He was also noted to have bilateral undescended testes. He developed bilateral chylothorax at 3 weeks of age, which resolved with low long-chain triglyceride, high-medium–chain triglyceride formula milk.

Investigations were initiated to determine the cause. Creatine kinase was 228 U/L. An MRI of the brain and spine revealed no evidence of hypoxic ischemic injury or other congenital structural abnormalities. Metabolic investigation results were negative. Microarray analysis revealed Xp21.1 deletion (dystrophin deletion) with loss of exons 46 to 52 out-of-frame deletion indicative of DMD. However, this was not suspected to be the cause of his neonatal hypotonia and ventilator dependence. A pyridostigmine trial pending results of acetylcholine receptor and muscle-specific tyrosine kinase antibodies revealed no significant response and the results were negative (Fig 1). Test results for *SMN* gene and myotonic dystrophy were negative. An open muscle biopsy histology done at 39 weeks' corrected age revealed diffusely abnormal and centrally

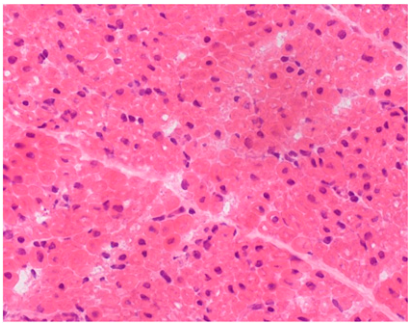

FIGURE 2
Hematoxylin and eosin stain revealing transversely oriented muscle fibers with centrally placed nuclei.

placed nuclei in the majority of the myofibers (Fig 2). This picture was highly suggestive of a congenital centronuclear myopathy. In addition, immunohistochemistry revealed a complete loss of dystrophin expression with an absence of staining in dystrophin 1, 2, 3 to rod C and N terminus (Fig 3). Electron microscopy revealed fibers with central nuclei, some with central glycogen, and also revealed proliferation of transverse tubules (Fig 4). Genetic tests confirmed XLMTM. The mutation was c.1189dupT p.Tyr397fs and results in a premature termination of the MTM1 protein and is predicted to be pathogenic.

The patient's parents were counseled extensively regarding the 2 genetic conditions in the infant that would significantly affect his quality of life. After several multidisciplinary team meetings, a joint decision was

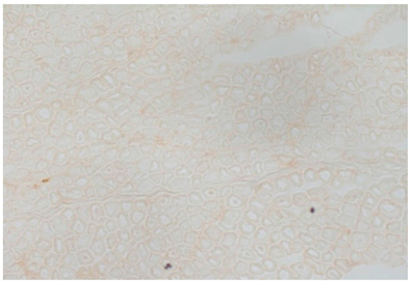

FIGURE 3
Immunohistochemical stain for dystrophin revealing a negative reaction.

undertaken by the medical teams and parents for reorientation of care, and the infant died at 2½ months of age. Both parents had genetic investigations that revealed that the mother was a carrier for MTM1 but not DMD. The father had no abnormalities detected.

DISCUSSION

Disorders of central and peripheral nervous system should be considered in floppy infants with ventilator dependence. An underlying neuromuscular disorder should be considered when there is evidence of hypotonia, weakness, feeding and swallowing difficulties, contractures, or multiple failed attempts at extubation.

Hypotonia of the neonatal period can be a result of central causes such as chromosomal disorders, hypoxic injury, metabolic disorders, or

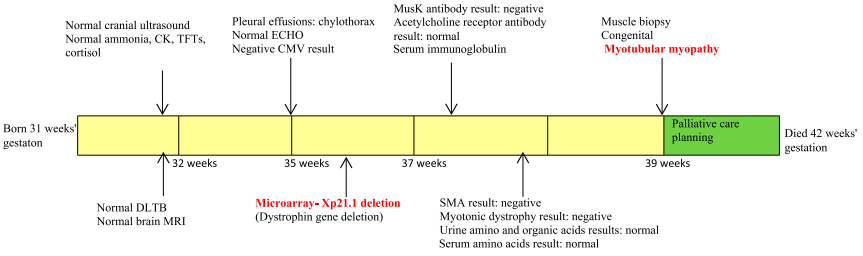

FIGURE 1
Time line of investigations. CK, creatine kinase; CMV cytomegalovirus; DLTB, direct laryngotracheal bronchoscopy; ECHO echocardiogram; MusK, muscle specific tyrosine kinase; SMA, spinal muscular atrophy; TFT, thyroid function test.

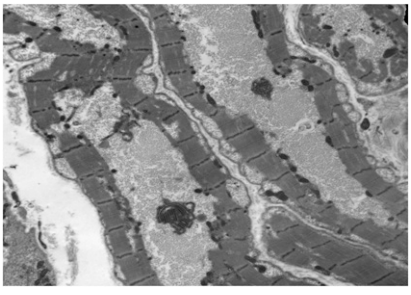

FIGURE 4
Electron microscopy image revealing fibers with central glycogen accumulation and electron dense tubules.

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because of peripheral neuromuscular disorders. A detailed family history, maternal history, and examination might reveal a diagnosis such as myotonic dystrophy or myasthenia gravis. Antenatal history of polyhydramnios and reduced fetal movements might be suggestive of a peripheral disorder. A comprehensive birth history is essential because prematurity and the condition of the infant at birth can influence the differential diagnosis. Clinical examination can reveal signs such as facial dysmorphism, facial weakness, tongue fasciculations, and a pattern of weakness, which would help in formulating differential diagnosis.

Investigations for congenital myopathies, congenital muscular dystrophies, congenital myasthenic syndromes, metabolic myopathies, spinal muscular atrophy, and Prader-Willi syndrome should be considered.[5]

Congenital myopathies are considered after investigating for the other more common conditions.[6] Genetic testing without muscle biopsy is undertaken only in special circumstances such as a severely ill infant or in withdrawal of care.[6] Creatine kinase, metabolic tests, acetylcholine receptor and muscle-specific kinase antibodies, tests for SMN1 mutation, myotonic dystrophy, and Prader-Willi syndrome were normal in our case. MRI of the brain did not reveal any evidence of hypoxia or structural abnormality. Although the microarray had picked up a significant diagnosis of DMD, it could not explain the clinical picture in this infant. Antenatal and early detection of mutation is possible in families with a history of DMD. Most cases are picked up after concerns of motor difficulties at a later age. The mean age of diagnosis of DMD in a 10-year retrospective study from a tertiary neuromuscular center in United Kingdom was 4.3 years.[7]

A muscle biopsy was undertaken at 54 days of life and 39 weeks' corrected gestation. Skeletal muscle development occurs throughout the period of embryogenesis. Dystrophin is expressed in the sarcolemma of most myotubes by 9 weeks' gestation. Marked changes occur in the structure and organization of muscle cells from 16 to 22 weeks and muscles look organized with fascicules of grouped fibers from 24 weeks' gestation.[8] The muscle biopsy specimen was suggestive of centronuclear myopathy and the lack of dystrophin expression also was in keeping with the Xp21 mutation.

To our knowledge, this is the first case report of an individual with a diagnosis of XLMTM and DMD. Both conditions are X linked but on different loci, with the former on Xq28 and the latter on Xp21. Both conditions are different in their pathogenesis and in the way they affect the muscles; this is evident in their natural history and histopathology. Congenital myopathy genes mostly encode protein components of the sarcomere and proteins involving calcium signaling with faulty gene causing ineffective muscle contraction. Muscle dystrophy genes mostly code for components of muscle membrane and extracellular matrix with faulty gene resulting in dystrophic muscle.[6]

In XLMTM, the infants present early in life with hypotonia, generalized weakness, and significant respiratory insufficiency needing ventilator support as we saw in our patient. More than half die of respiratory failure in the first year of life. In a recent, large multicenter study by Beggs et al,[9] 90% needed respiratory support at birth, nearly half of the patients required 24-hour ventilator support, and 60% needed tracheostomy, thus making it a severe form of congenital myopathy. There are case reports suggestive of chylothorax in XLMTM, but there is no definite explanation for this.[10]

Although the need for 24-hour invasive ventilatory support is uncommon in most congenital myopathies, XLMTM is an exception, and decisions on long-term ventilation have to be discussed in detail with the family.[11] In our patient, this discussion was crucial because of the accompanying diagnosis of DMD, which is a condition with progressive muscular dystrophy.

This case demonstrates how despite getting a positive result with the microarray, further tests had to be done because of a lack of correlation between the result and the clinical picture. This case also reflects sensitive discussions with the family on how the care of the infant could be oriented and emphasizes the importance of genetic counseling. We have described an unusual and rare combination of 2 X-linked muscle conditions in the same patient.

ABBREVIATIONS

DMD: Duchenne muscular dystrophy
XLMTM: X-linked myotubular myopathy

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DOI: 10.1542/peds.2018-2879 originally published online August 21, 2020;

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