Human Pathology: Case Reports (2016) 4, 4–8

ELSEVIER

Human PATHOLOGY Case Reports

http://www.humanpathologycasereports.com

# Congenital muscular dystrophy, cardiomyopathy, and peripheral neuropathy due to merosin deficiency: Peripheral nerve histology of cauda equina

Erika Hissong M.D.[a,1], Steven Salvatore M.D.[a,1], Kurenai Tanji M.D., Ph.D.[b,2], Ehud Lavi M.D.[a,*]

[a]*New York Presbyterian Hospital, Weill Cornell Medical Center, 525 E 68th Street, New York, NY 10065*
[b]*New York Presbyterian Hospital, Columbia University Medical Center, 630 W 168th Street, New York, NY 10032*

Received 27 February 2015; revised 21 May 2015; accepted 1 June 2015

**Keywords:**
Merosin;
Laminin;
Muscular dystrophy;
Peripheral neuropathy;
Cauda equina;
Neuromuscular disease;
Autopsy

**Abstract** Peripheral neuropathy, white matter abnormalities, and cardiomyopathy are associated findings with merosin-deficient congenital muscular dystrophy. Although characterization of the neuropathy with nerve conduction studies has been well documented, limited research has been able to correlate histopathology with nerve biopsy in humans. Our understanding of the mechanism, described as a demyelinating neuropathy, is mainly derived from mouse model studies. We report a 23-year-old male who succumbed to respiratory failure and ultimately cardiac arrhythmia in the setting of an uncharacterized end stage progressive muscular disease complicated by cardiomyopathy and severe scoliosis. Autopsy revealed extensive muscular atrophy and replacement by fibroadipose tissue throughout the skeletal muscle and myocardium. Immunohistochemical analysis of the muscle biopsy showed a complete loss of merosin. Thus, the cause for both his muscular disease and demyelinating neuropathy was established with the diagnosis of merosin-deficient muscular dystrophy. Nerve biopsy obtained from the cauda equina showed clear evidence of segmental demyelination and remyelination, providing a better understanding of the proximal peripheral nerve histopathological changes in this disease entity.


## 1. Introduction

Merosin, a heterotrimer also known as laminin-2, is an extracellular matrix protein composed of laminin-α2, β1 and γ1 chains, located in the basal lamina and linked to the transmembrane dystroglycan-associated glycoproteins. These glycoproteins in turn bind with dystrophin, which acts as a link between the extracellular matrix and the

* Corresponding author. Tel.: +1 212 746 2700.
*E-mail addresses:* emh9016@nyp.org (E. Hissong), Sts9057@med.cornell.edu (S. Salvatore), kt8@cumc.columbia.edu (K. Tanji), ehl2005@med.cornell.edu (E. Lavi).
[1] Tel.: +1 212 746 2700.
[2] Tel.: +1 212 305 4548.

http://dx.doi.org/10.1016/j.ehpc.2015.06.003

cytoskeleton, stabilizing the membrane during contraction [1–4]. Laminin 2 is expressed in various tissues, including skeletal muscle, placenta, peripheral nerve Schwann cells, and oligodendrocytes in the central nervous system. Up to 30% of children with congenital muscular dystrophy have been found to have mutations in the laminin α2 chain, which is encoded by the *LAMA2* gene located on chromosome 6q22 [2,3,5]. This is now referred to as merosin-deficient congenital muscular dystrophy (MDC1A). Clinical manifestations include severe hypotonia at birth, delayed motor milestones, weakness, early contractures, and elevated creatinine kinase [4]. In addition, involvement of tissues other than the skeletal muscle is usually present and can include cardiomyopathy, white matter abnormalities in the brain, and peripheral neuropathy [4].

Mouse models have shown that laminin 2, found in the complex S-merosin within Schwann cells, plays a critical role in peripheral nerve myelination [1]. Unfortunately, only limited data are available describing the histopathology of peripheral nerves seen in these patients, and there are no autopsy pathologic studies detailing proximal nerves. Thus, we describe the muscle, nerve and cardiac histopathology of an autopsy case of a MDC1A patient.

## 2. Case report

A 23-year-old white male was admitted to the medical intensive care unit for persistent non-bloody diarrhea and abdominal pain following a recent hospital admission for pneumonia, complicated by antibiotic-associated diarrhea. His past medical history was significant for congenital muscular disease, CNS dysfunction labeled as cerebral palsy, and cardiomyopathy, although a complete characterization of these diagnoses was never done. On admission, the patient was hypotensive (73/49), and laboratory testing was significant for hypocalcemia and an elevated lactate. *Clostridium difficile* toxin B by PCR was negative. CT scan showed an ileus pattern, with dilated small bowel loops, wall thickening of the transverse colon, and adhesions but no evidence of obstruction. Blood and stool cultures remained negative throughout the hospitalization. Shortly after admission, the patient developed respiratory distress requiring intubation. The patient remained hypotensive and acidotic despite intravenous fluids, dopamine, and a bicarbonate drip. On day four, he experienced a further drop in blood pressure (50/37) and was started on levophed, epinephrine, and vasopressin drips. He then went into ventricular fibrillation, which transitioned to asystole. The patient was pronounced dead following multiple unsuccessful rounds of cardiopulmonary resuscitation. An autopsy was requested after obtaining consent from the next of kin.

### 2.1. Neuromuscular examination

Gross examination was significant for extensive physical deformities, including severe scoliosis, contractures, and severe muscle atrophy. The muscles of the extremities were almost completely replaced by fibroadipose tissue. Representative sections of the relatively preserved diaphragm were obtained. Histologic examination revealed variation in muscle fiber size but lacked clear evidence of degeneration or regeneration of muscle fibers. Ragged red fibers were not seen on Gomori trichrome staining. There was no evidence of glycogen storage disorder or lipid accumulation with Periodic acid–Schiff and Oil Red O staining, respectively. Succinate dehydrogenase and cytochrome oxidase were also within normal limits. Representative semi-thin (Epon embedded, toluidine blue stained) sections of the cauda equina showed demyelinated and thinly myelinated large axons. Teased fiber preparations showed segmental demyelination and remyelination (Fig. 2). The brain could not be assessed, as the autopsy was restricted to exclude the brain.

An immunohistochemical analysis was performed on frozen sections of diaphragmatic muscle with a muscular dystrophy panel. Dystrophin was present, staining the sarcolemma of all muscle fibers. Immunostaining for dysferlin, alpha sarcoglycan, emerin, caveolin 3, and alpha dystroglycan was positive. Staining for utrophin had the normal distribution. The merosin stain in this patient was completely negative (while control staining was strongly positive), confirming the diagnosis of MDC1A (Fig. 1).

### 2.2. Cardiopulmonary examination

The cardiac examination was significant for a pericardial effusion (120 ml yellow, serous fluid), dilation of the right ventricle and left atrium, mild to moderate myocardial hypertrophy with extensive interstitial fibrosis and fatty infiltration on microscopic examination (Fig. 3). Due to severe skeletal deformity of the spine, the lungs were severely hypoplastic, weighing 218.4 g and 343.8 g, respectively (normal adult weights, right = 360–570 g and left = 325–480 g). Histologic examination showed diffuse bronchopneumonia and alveolar congestion and associated pleural adhesions were noted involving the chest wall and diaphragm.

### 2.3. Other organs

Other findings included hepatic steatosis, small intestinal adhesions, and focal large intestinal wall thickening, likely related to the recent antibiotic-related diarrhea. The kidneys showed focal areas of tubulointerstitial and glomerular scarring, out of proportion to the age of the patient.

## 3. Discussion

Although merosin deficient congenital muscular dystrophy and its association with peripheral neuropathy have been documented in the literature, and a sural (sensory) nerve biopsy was mentioned, detailed pathologic studies of motor nerves in

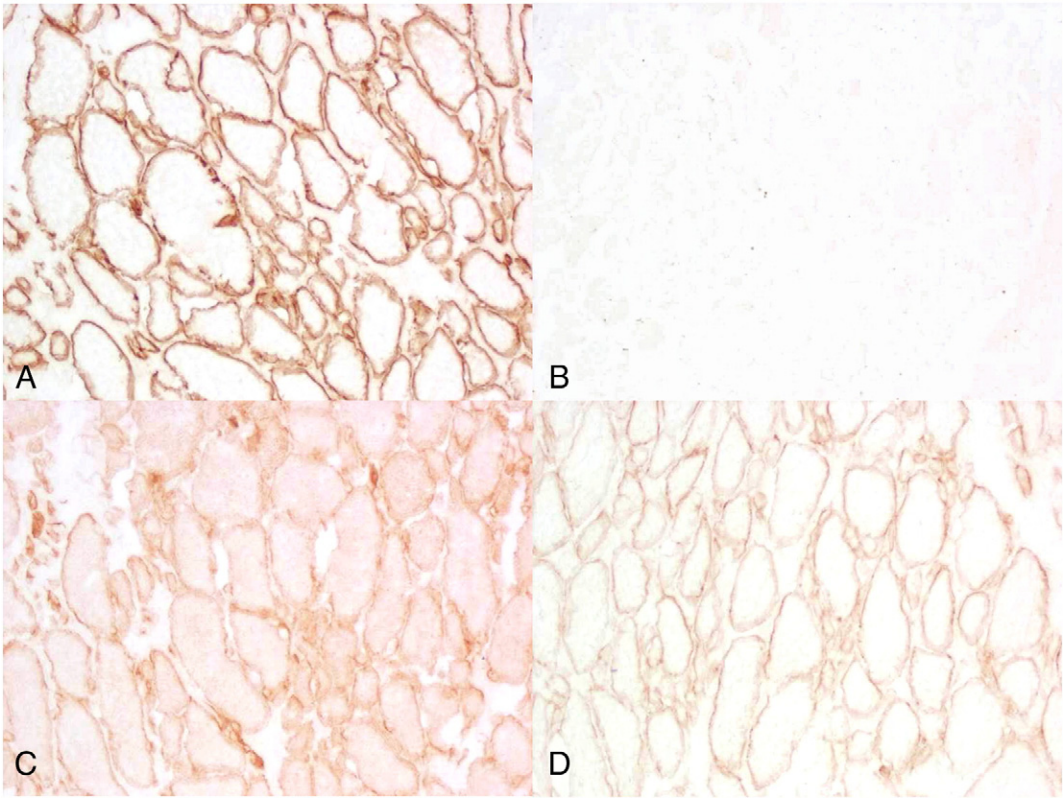


**Fig. 1** Immunohistochemical analysis of the diaphragm muscle frozen biopsy with muscular dystrophy panel. The sarcolemma of all muscle fibers was positive for dystrophin (A), dysferlin (C), and alpha-sarcoglycan (D). The muscle fibers were completely negative for merosin (B).

humans are lacking. To our knowledge, there have been no studies to date that have been able to capture the histologic features of axonal demyelination in the proximal nerves of the peripheral nervous system. The report that documented sural (sensory) nerve pathology did not exhibit clear demyelination and remyelination features and reached a conclusion that the myelin damage is a dysmyelination process rather than an active demyelination [3]. The present report aims to characterize the pathologic features of a nerve biopsy obtained from the cauda equina, which shows clear evidence of an ongoing segmental demyelination and remyelination.

MDC1A and the severity of its clinical presentation are dependent on the amount of merosin found in the musculature, as complete absence correlates with the most severe phenotype [6,7]. Individuals with absent merosin rarely achieve the ability to walk independently [6,8]. Genetic analysis of MDC1A

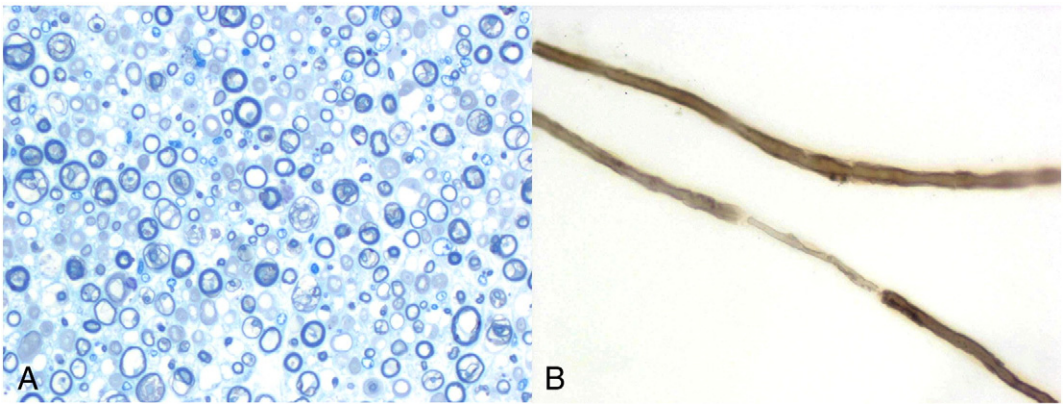


**Fig. 2** Histological findings of the cauda equina nerve biopsy. A: Semi-thin (1 micron) section of toluidine stained plastic embedded section of cauda equina nerve. The specimen shows variation in myelination of the nerve axons, with demyelinated and remyelinated (thinly myelinated) fibers. B: A teased fiber, silver stained preparation shows a short interval of segmental demyelination, separated from the remaining, appropriately myelinated nerve by the Nodes of Ranvier.

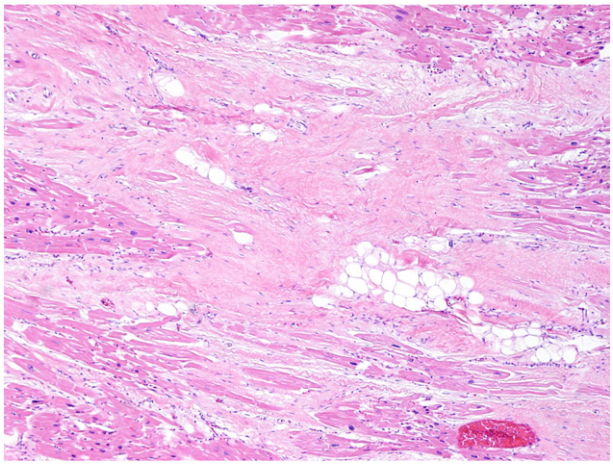

**Fig. 3** Histologic findings of cardiac muscle of the right ventricle exhibiting extensive cardiomyopathic fibrosis.

patients has identified mutations scattered throughout the *LAMA2* coding region, including missense, nonsense, deletion, or insertions. Nonsense mutations were associated with a more severe phenotype and complete absence of merosin [6,9].

Not only do skeletal muscles show phenotypic abnormalities, but sites other than the skeletal muscle are often affected as well, including the brain, heart, and peripheral nerves. White matter abnormalities seen on brain imaging have been described, with periventricular and subcortical white matter being two areas particularly susceptible. These abnormalities typically are asymptomatic, although there does appear to be an association with epilepsy, low IQ, and mental abnormalities [10]. The specific cause is largely unknown but may be due to disorders of neuronal organization and arrest in myelination, as merosin is important for stimulating the migration of oligodendrocytes and influencing the development and cell attachment of neuronal cells [2,4,11]. Another hypothesis suggests that abnormalities in the blood–brain barrier lead to increased water content within the white matter, which is thought to be secondary to laminins being present in the basement membrane of blood vessels [10,12]. In a minority of cases, structural cerebral abnormalities can also be seen. Cardiac manifestations also occur and include congestive cardiomyopathy with a reduction in ejection fraction. Merosin, in association with dystrophin, localizes to the sarcolemma and transverse tubules of cardiac muscle and has been found to be absent in the myocardium both of mouse models and upon postmortem examination in humans [4].

Much of the knowledge regarding the pathophysiology of peripheral nerve involvement has been gained through mouse model studies. Wei-Ming et al. described the importance of laminins in the peripheral nervous system by looking at several mutant strains of mice [13]. Another study also looked at both laminins and their receptors in Schwann cells in the context of hereditary neuropathy [9]. These studies found that laminins play a key role in both the central and peripheral nervous system. They are involved in axon pathway migration as well as nerve development. Specifically, laminins play an important role in the development of Schwann cells, as those lacking laminin expression no longer extend processes between axons [9]. This may partly be a result of impaired radial sorting, which prevents exposure of Schwann cells to axon-derived mitogens and therefore results in decreased Schwann cell proliferation [13]. Abnormalities in axonal radial sorting are seen in all types of laminin mutant mice and appear to be more severe in the proximal rather than the distal peripheral nervous system.

Histopathological examination of the nerves in these mouse models suggests that the process is one of demyelination, with patchy areas of axonal hypomyelination or naked axons, disruption of the endoneurium basal lamina, which is important for myelination, and shorter internodes with abnormally wide nodes of Ranvier [13]. These features appear to be most prominent in cranial nerves, dorsal roots, and proximal portions of peripheral nerves [2]. Most of the studies in humans have been based on electrophysiological studies, showing reduction of conduction velocities and action potential amplitudes [11]. Few studies have examined sural nerve biopsies for histopathological correlation, which support demyelination, but are limited in that they only can document the process in distal sensory nerves.

In summary, we present for the first time an autopsy case, which shows the histopathological manifestations of merosin deficient congenital muscular dystrophy in the heart and proximal portions of the peripheral nervous system which includes both motor and sensory nerves. This case highlights the importance of such features, as a demyelinating peripheral neuropathy can complicate the clinical picture and worsen the already severe effects this disease process has on the musculoskeletal system. By examining biopsies of the cauda equina, we were able to obtain a greater understanding of the extent of this neuropathic process and the severity in different locations throughout the nervous system. This knowledge will allow for better clinical correlation with phenotypic manifestations and help guide clinicians further in proper management options and prognostic expectations of this disorder.

## Acknowledgments

The funding for this work was provided by departmental funds. No conflict of interest existed for any of the authors.

## References

[1] Shorer Z, Philpot J, Muntoni F, et al. Demyelinating peripheral neuropathy in merosin-deficient congenital muscular dystrophy. J Child Neurol 1995; 10(6):472-5.

[2] Deodato F, Sabatelli M, Ricci E, et al. Hypermyelinating neuropathy, mental retardation, and epilepsy in a case of merosin deficiency. Neuromuscul Disord 2002;12:392-8.

[3] Di Muzio A, De Angelis M, Di Fulvio P, et al. Dysmyelinating sensory-motor neuropathy in merosin-deficient congenital muscular dystrophy. Muscle Nerve 2013;27(4):500-6.

[4] Gilhuis H, Donkelaar H, Tanke R, et al. Nonmuscular involvement in merosin-negative congenital muscular dystrophy. Pediatr Neurol 2002;26(1):30-6.
[5] Chan S, Foley A, Phadke R, et al. Limb girdle muscular dystrophy due to LAMA2 mutations: diagnostic difficulties due to associated peripheral neuropathy. Neuromuscul Disord 2014;24:677-83.
[6] Geranmayeh F, Clement E, Feng L, et al. Genotype–phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. Neuromuscul Disord 2010;20(4):241-50.
[7] Mora M, Moroni I, Uziel G, et al. Mild clinical phenotype in a 12-year-old boy with partial merosin deficiency and central and peripheral nervous system abnormalities. Neuromuscul Disord 1996;6(5):377-81.
[8] Dubowitz V, Sewry CA, Oldfors A. Muscular Dystrophies and Allied Disorders III. Muscle Biopsy: A Practical Approach. 4th ed. Saunders Elsevier; 2013 308-13.
[9] Feltri M, Wrabetz L. Laminins and their receptors in Schwann cells and hereditary neuropathies. J Peripher Nerv Syst 2005;10(2):128-43.
[10] Mercuri E, Pennock J, Goodwin F, et al. Sequential study of central and peripheral nervous system involvement in an infant with merosin-deficient congenital muscular dystrophy. Neuromuscul Disord 1996;6: 425-9.
[11] Brett F, Costigan D, Farrell M, et al. Merosin-deficient congenital muscular dystrophy and cortical dysplasia. Eur J Paediatr Neurol Soc 1998;2(2):77-82.
[12] Fujii Y, Surgiura C, Fukuda C, et al. Sequential neuroradiological and neurophysiological studies in a Japanese girl with merosin-deficient congenital muscular dystrophy. Brain and Development 2011;33:140-4.
[13] Wei-Ming Y, Yu H, Chen Z. Laminins in peripheral nerve development and muscular dystrophy. Mol Neurobiol 2007;35(3): 288-97.