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

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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

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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